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IMMUNIZATION

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SECTION I

GENERAL

1. Introduction. Immunization programs within the Armed Forces are administered under the authority of AR 40–562/BUMEDINST 6230.1 Series/AFR 161–13. This publication is intended to provide additional technical and administrative instructions for the implementation of these regulations.

2. Military Immunization Program. Immunization is practiced in the Armed Forces to prevent disease which, by its occurrence, might interfere with the accomplishment of the military mission. It is intended to protect the health and overall effectiveness of the command, as well as the health of the individual. This is a military obligation, exception to which is granted only for medical contraindications. Service policies vary; for Army personnel only, any immunization required to protect the individual and to assure that military units can perform their missions anywhere in the world without the danger of serious disease will be administered to an individual with or without his consent. In accomplishing this, medical personnel are expected to use only that amount of force necessary to administer the immunization. Prior to any forceful immunization, an individual should be counseled concerning the reasons why he should submit to the required inoculation. If force is necessary, it would normally be provided by personnel acting under orders from the individual's unit commander (AR 600–20). For Air Force personnel only, disposition of those personnel who refuse immunization will be handled on an individual basis—the use of force is not authorized.

a. Immunization May Be Active or Passive.

(1) *Active.* In active immunization, antibodies are actually formed within the body in response to the antigenic stimulation of natural infection or of infectious agents or antigenic substances derived therefrom. In this type of immunity, a physical change is effected whereby a permanent immune pattern is created which is easily recalled by subsequent exposure to the antigens.

(2) *Passive.* In passive immunization, antibodies that have been preformed in humans or animals are injected into the body. No permanent immune pattern related to the diseases involved is established.

b. Kinds of Vaccines. Vaccines may contain attenuated live organisms as in the case of yellow fever and smallpox vaccines, or contain inactivated organisms as in typhoid vaccine, or products of organisms as in diphtheria and tetanus toxoids. The type of vaccine must always be kept in mind when determining how a vaccine will be used, since a single injection of a live vaccine properly prepared, stored, and used so that it retains required viability (potency) usually produces a fairly rapid, ample and lasting immune response. By contrast, a single injection of most inactivated vaccines may produce only a scarcely detectable response. The first injection, however, orients the body so that subsequent injections produce successively larger responses. It is for these reasons that immunization against typhoid fever, cholera, typhus, tetanus and other diseases for which nonliving vaccines are utilized is carried out by a series of injections.

c. Dosage, Interval Between Injections and Booster Injections. For a dose of vaccine to produce a significant response in a previously oriented individual, a minimum interval of time must elapse. This interval may vary with different vaccines. For example, two injections of combined tetanus and diphtheria toxoid given 1 week apart are essentially no better than the same amount given as a single injection, whereas two doses given 4 or more weeks apart result in a markedly increased immunologic response. The usual intervals between injections may be greatly extended without any apparent loss of effect. A complete reimmunization series, therefore, is not required with any vaccine merely because a scheduled injection is overdue; the missed dose should be administered and the series completed; a new series *should not be started.* The lapse of years since the initial series (properly recorded) of any of these immunizing agents does not necessitate repetition of the initial series even when stimulating doses have not been given in the interim; a single stimulating dose only need be given. While the first or primary injection of an inactivated vaccine ordinarily must be in a fairly high dosage to establish the desired state of orientation, the required size of subsequent or booster doses

usually can be smaller. In a previously immunized individual, small booster doses may be capable of eliciting marked immunological responses.

d. Duration of Immunity.

(1) *Active.* The duration of effective immunity obtained with different immunizing agents varies with the effectiveness of the agent and the response of the recipient; therefore, it is not possible to define exact limits of duration. The immunizing schedules established in AR 40–562/BUMEDINST 6230.1 Series/AFR 161–13 are based upon the best evidence available and have been made conservative for the purpose of assuring successful immunization of nearly all individuals.

(2) *Passive.* The duration of passive immunity is never long-lasting, usually no longer than a few weeks and depends entirely upon the persistence of injected antibodies (approximately 7 days for those of animal origin; 30 days or longer for human antibodies). Asymptomatic infection can sometimes occur when passive immunity has fallen to a low level; this then results in prolonged active immunity. Normally, however, no permanent immune pattern related to the disease involved is established. On the other hand, if the serum of a nonhuman species is involved, a permanent specific hypersensitization often is established as the only lasting effect. When this develops, the foreign antibodies are rapidly removed from the circulation, and there is risk of serious reactions to future administration of serum from that (or related) animal species. However, passive immunization is a useful and indeed necessary procedure in specific emergencies. Passive immunization is often employed to prevent hepatitis, rabies, pertussis in babies, measles in contacts, and tetanus in unimmunized wounded individuals.

3. Standards, Distribution, Shipment and Storage of Prophylactic Biologicals. *a. Standards.* All biologicals obtained in this country for general use in the Armed Forces conform to the Public Health Service Regulations for the production and sale of such materials. Immunizing agents procured from sources not licensed by the Department of Health, Education and Welfare will meet standards acceptable to the National Institutes of Health or the appropriate Armed Service Investigational Drug Review Board. If procured abroad, these products must conform to standards at least equivalent to those of the Public Health Service Regulations. Expiration periods are based upon comprehensive experience and study of the rate at which specific biologicals lose immunizing potency. Based on the surveillance and assay of storage lots, potency periods (dating) may be curtailed or extended (under very specific limitations) by the appropriate Surgeon General. See appendix A for the list of the biological materials, their Federal stock numbers, unit of issue, volume and/or dose, potency periods and storage temperatures, on the military supply list in April 1970. For the current listing, see the current issue of Federal Supply Catalogue, Identification List C–6505–IL.

b. Distribution. Methods and procedures for distribution are described in AR 40–562/BUMEDINST 6230.1 Series/AFR 161–13. Biological products should not be stored in quantities so great as to preclude their use before the date of expiration.

c. Shipment and Storage.

(1) Yellow fever vaccine should always be shipped and stored at freezing temperatures (below 0°C. or 32°F.). The diluent (isotonic sodium chloride), which is packed separately, should not be frozen.

(2) Poliovirus vaccine, live, oral, requires particular care to preserve its potency. Prolonged storage should be in the frozen state at a temperature below —5°C. (23°F.). If maintained at these temperatures, the vaccine will retain satisfactory potency for a period of 1 year. In all instances the storage requirements indicated on the package will be followed. Once opened for use, the thawed vaccine should be kept at a refrigerator temperature between 2°C. and 8°C. (35° and 46°F.); in the refrigerator at this temperature, antigenic effectiveness of the vaccine is maintained without significant loss for a period of 7 days. An unentered container of vaccine may be used after as many as 10 thaw-freeze cycles, provided the temperature during thaw period did not exceed 8°C. (46°F.), and the total cumulative thaw time does not exceed 24 hours. If the 24 hour period is exceeded, the vaccine must be used within 30 days (stored at a temperature no higher than 8°C.).

(3) All other biologicals referred to in this publication should be stored at temperatures between 2° and 8°C. (35° to 46°F.). Lower temperatures should be avoided since freezing may result in damage to the product or to the container of diluent which may be packaged with a freeze-dried product. Unlike oral attenuated poliovirus or yellow fever vaccines, most biological products are relatively stable and do not necessarily lose their potency if kept at ordinary outdoor or room temperatures (1° to 35°C. or 33° to 95°F.) for periods up to 1 week. If, because of the exigencies of the service, they have been unavoidably stored or shipped at these higher temperatures, they may

be used with reasonable assurance of their potency provided they show no signs of physical change. In instances of exposure, even brief, to extremely high temperatures, as might occur through contact with steam radiators or proximity to open fire, the material should be suspended from use pending investigation (para 5, AR 40–562/BUMEDINST 6230.1 Series/AFR 161–13). Every attempt should be made, however, to ship and store these biologicals at the proper, recommended temperature conditions. Deviations should be permitted only when refrigeration cannot possibly be achieved. No deviation should ever be permitted in the case of yellow fever and oral poliovirus vaccines.

4. Precautions To Be Taken When Administering Biologic Products. *a. Principles.* The military immunization program is based upon the principle that the parenteral injection or oral administration of any antigen should be carried out only when the benefit to be derived clearly outweighs any significant risk. Because of the possibility of adverse reactions, the established doses and the schedules recommended herein should not be exceeded except in the presence of a clearly overriding indication, in which case the appropriate Surgeon General will be notified and informed of the circumstances in accordance with AR 40–562/BUMEDINST 6230.1 Series/AFR 161–13. The immunization program requires the administration of many biological preparations to a large number of individuals. As some individuals may be expected to show reactions of varying degrees due to sensitivity to the substances injected, all medical officers and all other personnel concerned with administering immunizations should be impressed with the possible seriousness of such reactions and the precautions to be taken to prevent them.

b. Types of Reactions. Injection of a substance into the human body is never without risk of injury; however, this risk can be reduced to a minimum through understanding and applying sound medical principles. The types of injury or reaction which may result from injection of biologic products are as follows:

(1) *Toxic.* Some vaccines after a period of several hours to a day or two may produce local reactions (induration, erythema, and tenderness) at the site of the injection, often accompanied by systemic reactions consisting of fever, headache, malaise, chills, gastrointestinal upset and other related symptoms. Whether these reactions are toxic in nature or based on sensitivity to some ingredients of the vaccine is not known. Symptomatic treatment with antipyretic and analgesic drugs and rest is usually adequate.

(2) *Allergic.* These reactions usually follow the use of products prepared in eggs, such as typhus, yellow fever and influenza vaccines, and to products containing horse serum, such as tetanus antitoxin and antirabies serum. Allergy to agents such as tetanus toxoid and typhoid vaccine has been reported, but is extremely unusual and in general indistinguishable from toxic reactions. However, the possibility of the existence of such allergies must be kept in mind and the necessary precautions taken.

(*a*) Allergic reactions vary in nature, severity and time of onset. Acute anaphylactic reactions occur within minutes after injection; these are characterized by circulatory collapse and respiratory embarrassment. They may lead rapidly to death if not treated vigorously and without delay. In addition to acute responses, local or systemic subacute allergic reactions may also occur, as well as reactions such as serum sickness which include certain characteristics of both the acute and subacute variety.

(*b*) A careful history of allergies and reactions should always be obtained from individuals about to receive injections and, where the possibility of an allergic reaction is found to exist, the injection should be postponed pending further investigation. For example, those with allergic symptoms on exposure to horses may be dangerously sensitive to horse serum. When administration of horse serum or other foreign serum is indicated, a careful history specifically directed at the possibility of sensitivity to the animal or animal serum must be taken, and, if positive, a skin test performed (see (*d*) below). In all instances, the patient's tolerance of small doses of the undiluted serum must be established prior to administering full doses, irrespective of the skin test findings.

(*c*) Individuals who give a clear-cut history of sensitivity to an immunizing agent should, with rare exceptions, be exempted from that immunization. Persons who cannot eat eggs, egg products, or chicken should under no circumstances be given vaccine prepared by cultivation in eggs (influenza, typhus, yellow fever, measles, or mumps vaccine; duck embryo rabies vaccine). Skin testing to determine the presence of allergy should be undertaken only under special circumstances. (See paragraph 7, AR 40–562/BUMEDINST 6230.1 Series/AFR 161–13, regarding exemption from immunization.)

(*d*) If, for some overriding reason, the decision is made to undertake vaccination of an egg-or-chicken sensitive individual, he should first be skin-tested by a scratch through a droplet of a 1:1000 dilution in saline of the vaccine, taking the usual precautions of having a syringe filled with

1:1000 epinephrine; (FSN 6505–853–4792 Epinephrine Injection, USP, 1:1000, cartridge needle unit, 1 cc.) and a tourniquet immediately available. In addition, the patient should, if possible, be in an emergency ward with a tracheostomy set immediately available. The scratch should be made on the distal portion of the extremity; in case of a reaction the tourniquet can then be applied and epinephrine injected locally as well as systemically. If there is no local reaction after 20 minutes, an intradermal skin test with 0.02 ml. of the 1:1000 dilution should be performed; if negative, repeat with a 1:100 dilution and, if negative again, with a 1:10 dilution. The same observation time periods pertain. If negative to a 1:10 dilution, a subcutaneous test dose of 0.2 ml. is given. If no adverse reaction occurs in 30 minutes, vaccination may be performed, and the individual is observed for reactions for at least one-half hour following the injection. *If a positive reaction is obtained to the 1:1000 or 1:100 dilution, vaccination should not be attempted.* If positive to a 1:10, with a typical urticarial wheal with sharp advancing borders, *vaccination may be attempted with utmost care, only if the need for such vaccination is considered sufficiently great.* The vaccine can be given in one-half the usual dose on successive days, 6 minutes after injecting 0.1 to 0.2 ml. of 1:1000 dilution of epinephrine in a second location. In this situation the risk of death from the disease against which the vaccine is intended to protect should very seriously be weighed against the risk of death from administration of the vaccine, before deciding to proceed with the vaccination. *If a systemic reaction results from the skin testing procedure, under no circumstances should the vaccine be administered.*

(*e*) An individual who demonstrates sensitivity should have appropriate entries made on his immunization records and his medical warning tag (AR 40–15/BUMEDINST 6150.29/AFR 160–21). Such entries constitute a recommendation that he should be exempted from the incriminated immunization and must be based upon a reliable history of, or a demonstrated sensitivity to, the immunizing agent. It is to be noted that immunizations required by international quarantine procedure cannot be waived; personnel not meeting international quarantine requirements may be subjected to such isolation, surveillance, or detection as responsible health authorities of countries of destination or intermediate point may prescribe. Air Force personnel unable to take smallpox, yellow fever or cholera vaccinations for medical reasons will be presented to a medical board as medically unsuitable for worldwide duty (para 9*b*, AFR 161–13).

(*f*) Passive immunization with hyperimmune horse or other animal serum leads to a significant incidence of serum sickness, characterized by an incubation period of 6 to 12 days, longer in some instances and shorter in those who have had previous immunization with serum from the particular animal. Serum sickness is manifested by pruritus, skin eruptions, (urticaria or erythema multiforme), enlargement of lymph nodes, fever, edema and polyarthritis and is distinctly different from the immediate shocklike and sometimes fatal anaphylactoid reaction. In persons not previously exposed to serum, the incidence of serum sickness is largely a function of the quantity of foreign serum injected. If 100 ml. or more are administered, 90 percent or more of the patients will show reaction. The usual prophylactic doses, however, of the purified and concentrated antisera result in serum sickness appearing in about 4 or 5 percent of patients after the first injection and more frequently with subsequent injections of serum from the same species. When there is known sensitivity to horse serum and antiserum (for example, antirabies serum) and administration is required, every effort should be made to obtain serum prepared in man or in another animal species. If this cannot be obtained, proceed as in (*d*) above, starting with minute amounts and giving increasing doses at 20 to 30 minute intervals ("desensitization").

(3) *Infection.* Immunization reactions can be the manifestation of infection with a microbial agent which is a component of the vaccine, or a contaminant introduced into the product by mishandling.

(*a*) The effectiveness of live vaccines, such as measles, poliomyelitis and yellow fever, derives from active immunity resulting from subclinical infection. The agent is attenuated to the point where it produces no, or only minimal, symptoms in the normal host. Defective host resistance or unusual response may result in the appearance of symptomatic, and rarely even fatal, disease. This is minimized by appropriate precautions.

(*b*) Unclean technique or contaminated materials, including an improperly handled vaccine may result in either local or systemic infection, particularly with one of the cocci. In addition, where syringes or needles are inadequately cleaned or sterilized, or where multiple doses are given using the same syringe, there is serious danger of inducing viral hepatitis (TB MED 206/AFP 160–5–6). If the jet injector cannot be used, an individual sterile needle and syringe should be used for each injection. Proper cleaning, sterilization of equipment and storage should be carried out. Where dry heat steriliza-

tion or autoclaving is not practical, continuous boiling for a minimum of 20 minutes may be used. Timing should begin after the last item is added and after boiling has started. Chemical sterilization is not effective (TB MED 78).

(4) *Cyst formation.* With vaccines containing adjuvants such as alum, so-called antigenic cysts or "chemical abscesses" may appear at the site of inoculation, even after the lapse of several months. Such cysts are "cold" and usually nontender, and may contain fluid with a very high antibody content. They generally resolve slowly and seldom require surgical intervention; if they become fluctuant, it is preferable to remove the fluid with a syringe and needle.

c. Management of Emergencies. A physician should be physically present or at a nearby, specified place known to the vaccinator whenever injections are being given. An allergy emergency kit should be on hand for the immediate management of serious reactions. This should include epinephrine for injection, epinephrine or Isuprel for inhalation, an injectable antihistamine, injectable aminophylline, water soluble corticosteroid esters such as cortisol succinate, injectable vasopressors such as metaraminol bitartrate or levarterenol bitartrate, injectable anticonvulsant drug such as amobarbital sodium, parenteral fluids such as 5 percent dextrose in saline with infusion tubing, sterile syringes and needles, a tourniquet, adhesive tape, alcohol swabs, oxygen, airways (several sizes), a tracheostomy set, suction apparatus, mechanical ventilator, and a "cut-down" kit. All personnel administering vaccine must be capable of instituting cardiopulmonary resuscitation. While sensitivity reactions occur only in a very small proportion of the individuals and are usually mild, they may on rare occasions be of sufficient gravity to require prompt action and may result in death within a few minutes if proper action is not undertaken. It is obligatory that all personnel administering immunization be familiar with the signs and symptoms of acute allergic reactions and be prepared to cope with them immediately. This obligation cannot be circumvented by any device such as the admixture of adrenalin with the vaccine; this merely may delay a serious reaction so that it occurs at a time and place remote from immediate medical assistance.

(1) *Essential preparations for possible emergencies.* Wherever an injection is given, an emergency tray should be conveniently located near at hand; a tourniquet should be on the tray, together with a 1:1000 solution of epinephrine in a syringe ready for use. (This standard disposable unit should be used—FSN 6505-853-4792, Epinephrine Injection, USP, 1:1000, cartridge-needle unit, 1 cc. 20's.) Severe reactions usually (although not always) occur immediately, whereas milder ones generally are delayed. The most common symptoms of acute generalized allergic reactions are dyspnea, cyanosis, retrosternal or lumbar pain, collapse and, sometimes, a rapidly extending urticaria. Collapse and shock coming on within 1 or 2 minutes after injection have a most serious significance and must be treated vigorously; this must be differentiated from fainting as an emotional response, in which the pulse is full and slow. The rapid development and extension of urticaria may be the first indication of a severe reaction.

(2) *Observation of inoculated personnel.* Since severe reactions may not develp for 15 to 20 minutes after injection, it is important to arrange personnel movements so that inoculated personnel will not leave the inoculation area for at least 10 minutes after injection, and will be no more than 4 or 5 minutes transportation time away from the area during the first 30 minutes after inoculation.

(3) *Immediate first aid. Immediately give 0.5 ml. epinephrine 1:1000 subcutaneously in any available area without stopping to prepare the injection site.* Put a tight tourniquet proximal to the injection site (on the side toward the heart) to prevent further absorption of the material, and get the patient under a physician's care as rapidly as possible. If the symptoms do not lessen after the subcutaneous epinephrine, the physician should give an additional 0.5 ml. epinephrine intravenously, using the femoral vein if required. Dilute the 0.5 ml. of epinephrine for intravenous injection to 10 ml. with sterile saline before injection. If the patient fails to respond to this within 3–4 minutes, intracardiac injection of 0.5 ml. epinephrine should be administered. After severe reactions, constant attendance for the first 24 hours, with a constantly running intravenous drip, is mandatory, since secondary lapses into shock may occur at any time. The tourniquet should be released with caution since a recrudescence of the reaction may develop as more antigen is absorbed.

(4) *Other measures.* Other measures which may be required are artificial respiration, intravenous norepinephrine to maintain blood pressure and the use of general supportive measures such as oxygen, suction and warmth. A tracheostomy set should be available since the majority of fatalities, reported involve asphyxiation due to laryngeal edema. Intravenous antihistaminics given after administration of epinephrine may be helpful. Intravenous hydrocortisone may be indicated during ensuing hours. If an individual has a dan-

gerous allergic reaction to any biologic agent or drug, the date, type, and severity of the reaction will be recorded in the space provided on the appropriate Immunization Certificate (PHS Form 731) and Health Record—Immunization Record (SF 601). For Air Force personnel, an entry will also be made on DD Form 722 as required by paragraph 3–18*a*(14), AFM 168–4; in addition, those units having a mechanized CBPO will enter sensitivity information on AF Form 1711.

d. Examination of Vial and Contents. Prior to the administration of any biological product, careful inspection of the label and contents is necessary to insure that the proper product and dosage is being used and that the contents are properly suspended and normal in appearance. Any discernible physical alteration justifies withholding the product from use.

e. Records and Reporting. Whenever local or constitutional reactions of unexpected severity or frequency occur following the injection of any biological product, further administration of that lot of vaccine will be discontinued and a report will be made in compliance with AR 40–61/Navy: FMSO-FLDBR BUMEDINST 6700–16 Series/ Air Force: Chapter 6, Volume V, AFM 67–1. The Department of Biologics Research, Walter Reed Army Institute of Research, Washington, D. C., 20012, has been designated to serve as a reference laboratory for the Armed Services for matters pertaining to biologicals. The processing of cases reported by Army, Navy and Air Force activities will be materially expedited by the submission directly to that agency of an information copy of the report and samples, shipped under refrigeration, of both opened and unopened packages of the suspected biological product.

5. Techniques of Administering Vaccines. *a. Needle and Syringe.* A separate sterile syringe and needle should be used for each individual to prevent transmission of hepatitis virus. Disposable syringes and needles are preferred. Care should be taken that the proper dosage is administered. To facilitate this, syringes of 3½ ml. capacity or less should be used. Vaccine injections (including intradermal) should be given in the back of the upper arm (triceps area) after the site has been prepared by use of a suitable cleaning agent (ether, acetone, or alcohol).

b. Jet Injection. See appendix A for vaccines which may be used with jet injector. When the jet injector (FSN 6515–656–1021 Hypodermic Injection Apparatus, Jet Automatic, 110 V. 60 c, AC, or 6515–910–0097 Hypodermic Injection Apparatus, Jet Automatic, Foot operated) is available, large number of men can be processed rapidly with minimal hazard of transmitting infection. While the nozzle is not sterilized between recipients, there has been no evidence of serum contamination or of transmitted disease. With some vaccines, there may be a greater local reaction than follows syringe-and-needle injection, but there is no difference in incidence of systemic symptoms. Instructions for its operation accompany the unit and should be studied by all operators. Critical elements in correct operation are as follows:

(1) The front end and parts in contact with the vaccine, including the piston and the feed needle must be sterilized. This is done by autoclaving at 15 lbs. pressure (250°F.) for 15–20 minutes (higher temperatues will damage the plastic seals), or by boiling for 20–25 minutes.

(2) Complete freedom of air from the system, evidenced by a sharp cutoff when the priming stream of sterile saline is ejected into the air, is essential for penetration of the skin.

(3) Priming is usually performed at the 0.5 ml. setting. If a different dose of the vaccine is required, the injector is set at this dose *after* the saline has been purged by ejecting two doses of the vaccine (a live vaccine should be fired into a thick alcohol-soaked gauze pad).

(4) A clean area of skin in the triceps area is selected. The site is sponged with acetone (or alcohol) and *permitted to dry.* If the arm is wet, the injector may slip during ejection of the stream, resulting in a cut. After the skin has dried, the nozzle of the cocked ejector is held firmly against the arm, the trigger squeezed and the pressure on the arm maintained for a count of three.

(5) If the injection site bleeds, a pledget of cotton should be firmly applied, since oozing may continue for several minutes.

(6) The injector is flushed with sterile water or saline before rest periods, to prevent settling of particulate material and caking. At the completion of use, the parts are flushed with clean water (saline will cause rusting).

6. Administration of Attenuated Living Vaccines. *a.* The longest duration of effective immunity follows recovery from infection with the causal organism of a disease. By selection of related organisms producing only localized disease (smallpox), or by the laboratory development of attenuated or avirulent mutants (yellow fever, polio, measles, mumps, rubella) or by the administration of an organism through an unusual route (adenovirus), it is possible to administer living organisms to healthy individuals, producing an asymptomatic

or very mild infection which evokes immunity analogous to that which follows the natural disease.

b. The attenuated organisms multiply until the host develops immunity to them. Therefore, it has generally been recommended that, whenever possible, immunization with live virus vaccines be separated by at least one month lest superimposed reactions and diminished antibody responses might result from the antigentic competition if two or more live virus vaccines are given simultaneously. If, the host should be immunologically defective, multiplication of the attenuated strain may continue, resulting in severe and possibly fatal disease. Therefore, *attenuated vaccines should not be given parenterally in any instance in which an impaired immunological response might be predicted*; i.e., the individual should be in good health and free of febrile illness; there should be no disease of the reticuloendothelial system including leukemia, lymphomas or generalized malignancy; the patient should not be under any therapeutic regimen which inhibits the activity of immunologic mechanisms, such as steroids, alkylating drugs, immunosuppressive agents, antimetabolites or radiation therapy. Because of the hypothetical possibility that circulating virus might penetrate the placental barrier and infect the fetus with consequent fetal loss or defect, parenteral inoculation of attenuated vaccines is not electively performed during pregnancy. These considerations are of less importance with oral polio vaccine since the attenuated viruses very rarely penetrate through the mucous membrane.

c. Consideration must also be given to any possible effect of the attenuated living agent on existing subclinical disease of the host. Natural measles has an adverse effect on the course of tuberculosis. Therefore, the theoretical danger exists that the attenuated measles virus might produce an exacerbation of a tuberculosis infection in a person not on specific chemotherapy. The frequency, although rare, with which pertussis vaccine injection is followed by central nervous system symptoms argues against its concurrent administration with another potentially encephalotropic vaccine.

d. While separate administration of live vaccines at 30-day intervals is ideal, practical considerations involved in scheduling immunizations often make combined immunizations essential. Intermediate intervals are not desirable because interferon is produced by certain virus infections which might prevent immunity from a live virus vaccine. Thus, attenuated measles vaccine evokes circulating interferon which has been shown to interfere with primary smallpox vaccinations performed between the 4th and 20th day after the measles vaccine had been given. Interferon has been shown to circulate after the yellow fever vaccine, and it is present locally after smallpox vaccination. Field studies have been carried out with combined smallpox-yellow fever, and smallpox-measles vaccines without intensification of reactions; smallpox-measles-yellow fever, measles-mumps, polio-adenovirus and smallpox-BCG have been administered concurrently with no increase in reaction rate. Antibody levels tended to be somewhat lower after combined vaccines but the seroconversion rates in general were comparable to those seen after single administration of the antigens. However, when yellow fever and smallpox were *mixed* before administration, yellow fever conversion rates were lowered. When given separately but concurrently, the yellow fever conversion rate was equivalent to that found when yellow fever was given by itself.

e. Although the administration of gamma globulin together with measles and with mumps has been shown not to interfere with the development of immunity, pending further studies it is inadvisable to administer living vaccines after gamma globulin has been administered prophylactically, lest residual passive antibodies interfere with full antigenic stimulus. Likewise while passive maternal measles immunity usually lasts 6 to 9 months, measles vaccine should not be given before a child is 12 months of age lest, in some cases, residual maternal immunity interferes with the necessary propagation of attenuated measles virus so that no immunity ensues.

f. In summary, while separate administration of live vaccines at 30-day intervals is the theoretical ideal, the separate but concurrent administration of smallpox, yellow fever, oral poliomyelitis, and oral adenovirus vaccines is acceptable. These vaccines are best administered in two groups, first polio and adenovirus vaccines at the beginning of military service, followed by smallpox and yellow fever a month or more later. In the immunization of dependents, polio vaccine should be given in the first few months of life; measles and mumps vaccination should be delayed for one year because transplacentally transferred maternal immunity may interfere for nine to twelve months. Tuberculin testing is usually done at 11 months of age; since measles virus can aggravate active tuberculosis, it is theoretically preferable that tuberculin testing, followed by appropriate treatment if positive, precede administration of attenuated measles vaccine. However, when mass measles immuniza-

tion programs are carried out, tuberculin testing is not considered necessary.

7. Immunization Requirements for International Travel. *a.* By International Sanitary Regulations, travelers may be required to have been immunized against smallpox, cholera and/or yellow fever for entry into a country. For smallpox, primary vaccination is required not less than 8 days nor more than 3 years prior to arrival, or revaccination within 3 years. Cholera vaccine may be required for persons 6 months of age or over. The certificate is valid for six months beginning 6 days after the injection of vaccine, or on the date of revaccination if this was done within the 6-month period. Yellow fever immunization is required more than 12 days and less than 10 years prior to entry of all persons 6 months of age or older arriving in, or destined for, yellow fever receptive areas within 6 days of departure from areas infected with yellow fever. Military personnel are required to comply with these international requirements. These are met by standard military immunizaion when recorded on PHS Form 731, and validated by signature of the medical officer and by the official stamp. Specific area requirements vary; current requirements are found in the triservice directive on Immunization Requirements and Procedures: AR 40–562/BUMEDINST 6230.1 Series/AFR 161–13. For air travel, USAF Foreign Clearance Guide (AFR 5–30) revised semimonthly and available at all major and foreign clearing USAF bases, contains each country's immunization requirements. Reference to these publications is particularly necessary for personnel traveling through several countries en route to destination. Thus, one can travel from the United States to Thailand without being immunized against cholera; however, if there were a stop in the Philippines or in India, entry to Thailand would be forbidden unless there had been a cholera immunization within 6 months. In case the required immunizations have not been given, quarantine officers at ports of entry may place the traveler in isolation or under surveillance for the incubation period of the disease in question. If the traveler presents a physician's statement written on his letterhead that the vaccination is medically contraindicated for a stated reason, the quarantine officer may give this consideration. However, it must be noted that some countries have chosen to stand on the official requirement (para 4*b*(2)(*e*)).

SECTION II

ROUTINE IMMUNIZATIONS

8. **Smallpox Vaccine.** *a. General.* The only completely effective method for the prevention or control of smallpox is vaccination by proper technique with a potent vaccine. This procedure induces primary vaccinial infection ("vaccinia") in the completely susceptible subject. Residual immunity from previous vaccination will result in a modified vaccinial infection. Vaccinia is almost invariably a mild, self-limiting disease inducing immunity to smallpox for a variable period but almost always for at least 3 years. In the face of exposure to smallpox, however, to assure that they are adequately protected, all individuals should be revaccinated regardless of their previous history of vaccination, and yearly revaccination is advisable for those traveling or residing in endemic areas. Two vaccinations at an interval of 1 week should be scheduled; the second is not performed if an appropriate reaction is present. The effectiveness of proper smallpox vaccination has been conclusively proven by the eradication of this disease from all of the developed countries. During World War II, only 105 cases of smallpox occurred in United States military personnel in overseas theatres. These occurred particularly in the Orient where smallpox was prevalent among the indigenous population. Investigation disclosed that most cases occurred in persons who had vaccination failures due to improper technique or who developed sensitization reactions misinterpreted as true "takes." While great strides are being made in the eradication of smallpox under the World Health Organization Smallpox Eradication Program, the disease persists in several geographic areas; viz., the Indo-Pak subcontinent and Indonesia in Asia; much of Africa south of the Sahara, and Brazil in South America. The disease is periodically carried out of these foci to threaten if not cause epidemics in poorly immunized countries now free of disease. It is essential that a high level of immunity to smallpox be maintained in military personnel who might be called on to serve in foreign areas.

b. Material. There are two vaccines commonly in use in the United States. The Armed Forces are using only the freeze-dried smallpox vaccine supplies with reconstituting fluid. The freeze-dried material is preferred because of its greater stability on prolonged storage without refrigeration. However, even freeze-dried vaccine should be kept in the coolest available storage space, but, if necessary, it can be handled like inactivated vaccines. After the dried vaccine is reconstituted, it may be kept only for one month if held under normal refrigeration (4°C. or below), because, once reconstituted, it has the instability of the usual glycerinated vaccine.

c. Vaccination Age and Site. Primary vaccination can be carried out at any age. If performed in the neonatal period (in epidemic situations), the baby should be revaccinated after 6 to 12 months. Vaccinations in the 4 through 6 month period, while some residual maternal immunity persists, often result in mild reactions. Many recommend that vaccinations be deferred until the second year of life because the incidence of reported reactions is greater in the first year; however, when vaccination is carried out with 1 or 2 insertions in a thriving child, there is no contraindication to earlier vaccination. Vaccination should be performed on the arm over the insertion of the deltoid muscle. If grossly dirty, the site should be gently cleaned with water and dried before proceeding; energetic cleaning may create abrasions which may be infected to constitute "satellite lesions." If clean, no treatment of the skin is required. An antiseptic such as either or acetone (alcohol should *not* be used) may be applied and allowed to dry thoroughly; failure to allow the antiseptic to dry may result in inactivation of the vaccine.

d. Methods of Vaccination.

(1) *Multiple pressure.* A droplet of reconstituted freeze-dried vaccine is placed on the selected site, either using the supplied applicator, or, if bifurcated needles are supplied, by dipping the needle in the vaccine and touching this to the skin. The needle is held tangential to the vaccination site and the needle point is then moved rapidly through the droplet in a motion perpendicular to the skin, lifting the needle clear with each stroke. For revaccinations, about 30 pressures, (15 strokes with the bifurcated needle, since

each stroke makes two pressures) are made within a 5 or 6 second period. Pressure applied at this rate provide the optimal depth of penetration. For primary vaccination, 4 (or fewer) pressures are sufficient. The pressures are applied over an area no greater than 1/8 inch in diameter. Remaining vaccine is wiped off the arm with dry sterile gauze. A properly performed vaccination should not bleed freely, but the appearance of spots of blood after 20 to 30 seconds in the points of needle pressure is desirable. No dressing should be applied to the vaccinated area; if a weeping lesion later develops, the clothing is protected by a loose dressing, or by fixing one to the sleeve itself. No restrictions in normal activity, e.g., bathing, are indicated.

(2) *Multiple puncture.* If bifurcated needles are available, equally good or somewhat better results can be achieved by the multiple puncture technique. In this method, the needle is held perpendicular to the surface of the skin rather than tangential. The needle is dipped into the vaccine, the vaccine is placed on the skin at the point of deltoid insertion by touching the side of the point to the skin; then, with the needle held firmly, one or two (for primary vaccination); or 15 (for revaccination) firm pressures are made through the drop of vaccine restricting the punctures to as small an area as possible. This is facilitated if the subject places his hand on his hip and the vaccinator makes the puncture with wrist action, stabilizing.his position by resting the heel of his hand or a finger on the surface of the arm. The vaccine is wiped off and no dressing applied.

(3) *Jet injection.*

(*a*) When large numbers of individuals are to be vaccinated at one place in a short time, jet injection is the preferred method of administering the vaccine. Only smallpox vaccine which has been specially processed for jet injection (FSN 6505–926–4764) may be used. This is supplied in 100 dose bottles, together with 10 ml. of saline in a container with attached needle, and two alcohol sponges packaged in foil for cleaning bottle tops in reconstituting the vaccine and attaching it to the jet injector. The reconstituted vaccine contains only about 3 percent of the virus content of the vaccine used for multiple pressure vaccination, and therefore must not be used for other than jet injection.

(*b*) For smallpox vaccination, the jet injector must be equipped with the Nozzle, Automatic Jet Hypodermic Injection Apparatus (FSN 6515–913–7908) in place of the conventional nozzle. The intradermal nozzle cups the skin into a small mound and directs the stream tangentially into the skin. The desired intradermal dosage is 0.1 ml; the dosage adjustment of the injector should be set slightly higher to compensate for the drop of fluid which remains on the skin (a setting of 0.12 ml. is recommended). The injector is primed at a setting of 0.5 ml. with sterile saline or water to purge the system of air; when the stream has a sharp cut-off indicating absence of air in the system, the dosage is reduced to the 0.12 ml. level and the sterile solution fired into the air several times to assure proper action. When the vaccine is placed in the gun, it is preferable to fire into an alcohol-soaked gauze pad or cotton-filled container to minimize the risk of aerosol contamination of closed spaces.

(*c*) In reconstituting the vaccine, the top of the bottle containing the freeze-dried vaccine is cleansed with the alcohol sponge. The diluent container is held vertically and the needle pushed downward into the stopper. The vacuum will pull the fluid in. The diluent container must be held so that air is not permitted to enter the needle until all the fluid is transferred. If this has been properly done and transfer does not occur, the vacuum has been lost and the vaccine should be discarded as possibly deteriorated and unusable.

(*d*) The bottle containing the reconstituted vaccine is placed on the jet injector after the bottle top has been cleansed with the alcohol sponge and the apparatus fired into alcohol-soaked cotton at least five times so that vaccine replaces the priming fluid. The usual vaccination site over the insertion of the deltoid is cleansed with acetone or ether, permitted to dry, the nozzle firmly applied to the arm and the dose injected. A 3–4 mm. wheal usually appears; a pledget of sterile cotton should be applied to the injection site to control the occasional show of blood.

(4) *Disposable plastic vaccinator.* Disposable plastic vaccinators, together with the necessary vaccine, are provided under FSN 6605–935–3997. These vaccinators ("MonoVacc") have a group of nine plastic points in an approximately 2 mm square, mounted on a circular platform which is attached to a ring designed to fit over the thumb. Vaccine is applied according to the manufacturer's instructions to cover all nine points. The skin is prepared as above and the tips are then firmly pressed in with sufficient pressure that an imprint of the circular platform remains on the skin. When used for primary vaccination, a single pressure is used; for revaccination, three firm pressures are made into the same site. The remaining vaccine is wiped off and subsequent course is as above. In using this apparatus it is important that sufficient pressure is used. The applicators are dis-

carded after use (see *e* below); they cannot be sterilized by heating or by alcohol without damaging the tips.

e. Disposal of Used Freeze-Dried Smallpox Containers. The vial in which the vaccine was reconstituted and the assembly of the items for administration contain live virus. Before discarding these items they should be burned, boiled, or autoclaved to prevent accidental vaccination.

f. Vaccination Responses.

(1) If a potent vaccine has been properly employed the response will reflect viral multiplication, immunity, and cellular hypersensitivity. In the primary vaccination, a papule appears at the site of vaccination on about the third day. This becomes a vesicle on the fifth or sixth day, which becomes pustular, umbilicated and surrounded by erythema and induration. The maximal area of erythema is attained between the eighth and twelfth day following vaccination (usually the tenth). The erythema and swelling then subside and a crust forms which comes off about the twenty-first day. At the height of the primary reaction there is usually regional lymphadenopathy and there may be systemic symptoms of fever and malaise.

(2) The primary vaccination elicits immunity, which wanes after several years, and an allergic sensitization to viral protein which persists. This allergy is manifested by the appearance of a papule and a small area of redness appearing within the first 24 hours after revaccination; this may be the maximum reaction but not infrequently vesicles appear in 24 to 48 hours with ultimate scabbing. The peak of the reaction is passed within 3 days. This reaction follows the application of heat inactivated or fully potent vaccine equally well; with inactivated vaccine there is no increase in antibodies but with potent vaccine antibody rise occurs in roughly half of those who exhibit this reaction. As immunity wanes, revaccination with potent vaccine elicits this allergic response followed by the changes produced by propagating virus. The lesion may then go through the same course as the primary vaccination or reawakened immunity may accelerate the development of the lesion and its attendant erythema. Viral propagation can be reliably assumed to have occurred (and immunity evoked) when the greatest area of skin involvement (erythema) occurs after the third day after revaccination.

g. Interpretation of Vaccination Reactions.

(1) *General.* The objective of smallpox vaccination is to produce immunity which will protect against infection by variola virus. With primary vaccination, there is no difficulty in recognizing the typical Jennerian vesicle which is found on examination a week (6 to 8 days) after a successful vaccination. Any reaction 1 week after vaccination that shows a pustule, a vesicle, or an area of definite redness, induration and/or congestion surrounding the central lesion, regardless of its form, is a MAJOR REACTION, and indicates that virus multiplication has occurred with consequent development of immunity; the second vaccination is unnecessary. All other vaccination responses are termed EQUIVOCAL REACTIONS which, with good technique and good vaccine, often are abortive infections increasing the level of immunity; however, these may only be nonimmunizing allergic skin responses to vaccine inactivated by poor technique or poor handling. All personnel exhibiting equivocal reactions difficult to categorize by these criteria, should be immediately revaccinated using more vigorous technique and another properly handled vaccine lot. The immune individual will suffer no discomfort from the repeated vaccination other than local itching. Examination of the second *re*vaccination is normally not necessary, but failure of a *primary* vaccination attempt requires repetition and observation until a take is obtained.

(2) *Recording.* USPHS Form 731 requires that all primary vaccinations be read, the results recorded as "successful" or "unsuccessful," and vaccination repeated if unsuccessful. For revaccinations, international requirements only call for the recording of the date, the vaccinator, and the origin and batch number of the vaccine and whether it was liquid or freeze dried; the entry "Major" or "Equivocal" should be entered at the revisit, under the word "Revaccination," and, if equivocal, the date of the second vaccination attempt entered.

h. Adverse Reactions. A primary vaccinal infection is the expected proper reaction in an unimmunized individual and is strictly not an adverse reaction. Nevertheless, during World War II this resulted in the admission to Army hospitals of approximately 1.7 individuals per thousand. Such admissions were more frequent in the summer (3.3 per thousand during August as contrasted to 0.7 per thousand in January); most of them were due to severe, though uncomplicated, primary reactions. A very few, however, were due to genuine complications of which the most serious are postvaccinal encephalitis, eczema vaccinatum and progressive vaccinia.

(1) *Postvaccinal encephalitis.* This complication of smallpox vaccination is very rarely seen in

the United States. Only eight cases were reported during World War II and, on investigation, only four of these were consistent with the diagnosis. This condition usually develops suddenly 10 to 13 days after vaccination and is characterized by headache, vomiting, drowsiness, and spastic paralysis. The spinal fluid count is usually between 100 and 200 mononuclear cells per cubic millimeter. Case fatality rates as high as 40 percent have been reported; there are usually no sequellae in survivors. Because this complication is rare among U.S. personnel vaccinated by our methods, and since it is not possible to predict who might be afflicted, no preventive measures are indicated; vaccinia immune globulin is ineffective for treatment.

(2) *Eczema vaccinatum.* Eczema vaccinatum is the infection of eczematous skin with vaccinia virus; it is basically a problem of military dependents. This complication may be fatal; vaccinia hyperimmune gamma globulin has been shown to be useful in the treatment of serious, progressive cases of eczema vaccinatum; methisazone (Marboran, N-methylisatin 3 thiosemicarazone) may be life saving. Unvaccinated eczematous individuals should be kept away from vaccinated individuals for 1 week after a revaccination and 2 weeks after a primary vaccination to avoid development of eczema vaccination by contact. *Individuals with skin disorders such as eczema or atopic dermatitis should not be vaccinated routinely against smallpox.* An absolute indication for administering a smallpox vaccination to an individual with eczema is exposure to smallpox. In the rare instance where an individual with eczema must be vaccinated because of overseas orders, vaccinia hyperimmune gamma globulin (VIG) should be concurrently administered as a prophylactic. It may be obtained from the Division of Communicable Disease and Immunology, Walter Reed Army Institute of Research, from the 406th General Laboratory in the Far East, from the USAREUR General Laboratory in Germany, or through one of the Vaccinia Immune Globulin Consultants of the American Red Cross. Studies with an attenuated tissue culture strain of vaccine have given promising results when used for "prevaccination", preparing the patient for vaccination with a standard strain a few months later, and also protecting him from the danger of developing eczema vaccination by contact.

(3) *Progressive vaccinia.* This entity is very rare. It occurs in immunologically defective individuals. This defect may be congenital or the consequence of therapy with immunosuppressive or corticosteroid drug, radiation therapy, aplastic anemia, or tumors of the reticuloendothelial system, especially leukemia. Early treatment with high doses of vaccinia hyperimmune gamma globulin is indicated. Methisazone has been shown to be of value in half the treated cases.

(4) *Generalized vaccinia.* This is a benign self-limited disease characterized by vesicles which appear 5 to 10 days after vaccination. This entity appears to be rare in revaccinees, and is probably due to a transient viremia.

(5) *Exanthematous reactions.* A variety of skin eruptions of an allergic nature have been seen after smallpox vaccination. These include erythema multiforme, urticarial rashes, and morbiliform eruptions. These are generally self-limited with a favorable prognosis, but rare cases of severe bullous erythema multiforme (Stevens-Johnson syndrome) have been reported.

(6) *Autoinoculation vaccinia.* Vaccinia virus can be transferred from the vaccination site by the finger to mucous membranes or to abraided skin surfaces and initiate satellite lesions. These may result in scarring, but except for the rare instance where pre-existing excoriation permits infection of the cornea rather than the conjunctiva, this complication seldom has serious complications. In cases where vaccinia has been implanted on the conjunctiva or cornea, many experts recommend the use of IDU (5-iodo-2-deoxyuridine) although, at present, there are no data from control trials which assure its efficacy. Vaccinia immune globulin should not be given because these patients generally have good levels of antibody at the time the leisons are troublesome, and more may result in corneal precipitates and opacities.

(7) *Reactions to other vaccines.* Other vaccines, such as typhoid vaccine or tetanus-diphtheria toxoids, should not be injected into an arm in which a major reaction to vaccinia is occurring, because systemic reactions of chills and fever are more likely to occur. As long as no fever, or constitutional vaccinal reaction is present, there are no contraindications to such injections *in the nonvaccinated arm.*

i. Contraindications to Vaccination Against Smallpox. Vaccination in the United States should only be carried out on healthy individuals and deferred on those who are ill. However, in the face of a definite exposure to smallpox there are no contraindications to smallpox vaccination. Travelers with known contraindications to vaccination should be discouraged from traveling in endemic areas; if necessary, they may be vaccinated and given a prophylactic dose of vaccinia hyperimmune gamma globulin. The contraindications to administration of smallpox vaccine include—

(1) Acute Illness.

(2) Eczema or other severe dermatologic eruptions.

(3) Leukemia, lymphoma, and generalized carcinomatosis.

(4) Hypogammaglobulinemia or other deficiencies of the immune mechanisms.

(5) Corticosteroid or radiation therapy, or therapy with immunosuppressive drugs.

(6) Aplastic anemia.

(7) Pregnancy. Vaccinia virus has extremely rarely crossed the placental barrier producing fatal disease of the fetus or newborn child; of the 21 cases reported in the medical literature, virtually all instances have followed primary vaccination. Although the risks to the fetus or pregnant mother are extremely small, these risks need not be undertaken unless there is a much greater danger of potential exposure to smallpox.

(8) Infancy, age under 1 year, is accepted by USPHS as a medical contraindication, for purposes of entry into the United States.

9. Typhoid Vaccine. *a. General.* Vaccination against typhoid fever confers relative immunity which has been demonstrated to last 4 to 6 years in endemic areas. The effectiveness of current vaccines is related to degree of exposure to typhoid bacilli; best protection is demonstrated against a small dose challenge such as might be ingested from contaminated water, while large numbers of organisms which may be found in contaminated food may overwhelm vaccine-induced resistance. The continued inclusion of paratyphoid A and B organisms in a combined vaccine is not justified. These antigens increase the adverse reactions, and they have not been shown to provide protection against the paratyphoid fevers in the doses ordinarily used. Systemic disease (as opposed to the diarrheal disease) due to these organisms is infrequent. For these reasons, they have been eliminated from the vaccine. Protection against these infections depends mainly on proper sanitary measures related to food and water supply and waste disposal, as does control of typhoid fever.

b. Material. The typhoid vaccine produced commercially for the Armed Forces contains Ty2 strain of *Salmonella typhi* (10^9ml.), killed and dried with acetone to preserve its antigenicity. This type of typhoid vaccine (AKD) has proven to be effective in large-scale field trails and replaces the heat-phenol triple antigen vaccine (TAB-Typhoid, paratyphoid A and B).

c. Method of Vaccination. Initial vaccination with the acetone-inactivated dried vaccine consists of the subcutaneous or intramuscular injection of two 0.5 ml. doses of AKD typhoid vaccine in the triceps area at an interval of not less than four weeks. Revaccination is accomplished by injection of 0.5 ml. subcutaneously or intramuscularly (THE AKD VACCINE PRODUCES A MARKED LOCAL REACTION WHEN GIVEN INTRADERMALLY) and is required no more than twice at 4-year intervals during service in an area of low endemicity such as the continental United States. However, it may be administered more often if indicated by conditions of increased risk. In areas of high prevalence annual booster injections may be given. If heat phenol-treated TAB is in use, basic immunization is afforded by two injections of 0.5 ml. SC or IM, 4 or more weeks apart; booster doses of 0.5 ml. SC or IM or 0.1 ml. intradermally.

d. Reactions. The monovalent acetone-treated vaccine produces reactions similar to those following the heat-phenol typhoid-paratyphoid preparation. Local reactions are common (50–80 percent of recipients) and include local pain, erythema, induration and swelling; local reactions are more frequent when these vaccines are jet-injected than when injected by syringe and needle. Systemic reactions manifested by fever, myalgia, headache, and malaise, although less frequent (occurring in 10–20 percent) are troublesome. This frequency is not influenced by method of administration. The appearance of generalized reaction does not justify condemnation of a particular lot of vaccine unless there is marked disability in a significant number of individuals (25 to 30 percent). Most reactions can be alleviated and even prevented in susceptible individuals by salicylates if taken regularly following the vaccine administration. When practicable, typhoid vaccination should not be accomplished in conjunction with any other injection apt to produce a similar reaction, or during a febrile illness. Typhoid immunization should be avoided just prior to intensive physical activity, particularly when environmental temperatures are high.

10. Tetanus and Diphtheria Toxoids, Adsorbed (For Adult Use). *a. General.* This is the official name for the material now used for routine immunization against tetanus and diphtheria of military personnel and other eligible individuals (described below).

(1) This product (T–d) contains the usual immunizing amount of tetanus toxoid to which has been added a very small amount (1–2 Lf per

dose) of purified diphtheria toxoid (the usual pediatric immunizing dose of diphtheria toxoid ranges from 10 to 21 Lf). After injection of three properly spaced doses of such a combination, 95 percent or more of American adults are found to be immune to diphtheria; after two doses, 80 percent are immune. Such results depend partly on the booster response induced by small doses of toxoid, but also on the high antigenicity of present-day toxoids. These combined antigens eliminate the necessity for separate diphtheria and tetanus immunization as a routine procedure in adults.

(2) Routine immunization with tetanus toxoid is based upon the experience of the United States Armed Forces and foreign military services with active immunization against tetanus during World War II. The use of this product resulted in the lowest incidence of tetanus among wounded soldiers that has been observed in any war to date; only four cases of tetanus occurred during World War II among United States soldiers who had been fully immunized and had received an emergency booster at the time of injury (0.15 cases per 100,000 wounded). This experience stands in contrast to the rate of about 10 per 100,000 wounded in the unimmunized Japanese Army and Navy, and similar high rates in German soldiers and Philippine civilian casualties. When immunization is performed with the toxoids combined with a mineral adjuvant, a protective level of tetanus antitoxin persists for ten years or more. Responsiveness to a booster dose lasts for many more years.

(3) Because of the very small amount of diphtheria toxoid contained (1–2 Lf per 0.5 ml. dose), reactions due to sensitivity to diphtheria toxoid are infrequent. When immunizing adults against tetanus and diphtheria with a combined toxoid, care should be taken to insure that the preparation is labeled "for adult use"; adults frequently develop severe reactions to the pediatric preparations which contain 10 to 20 Lf of diphtheria toxoid per dose. The adult preparation, however, can be used for primary or booster immunization in school-age children (defined as over 6 years of age, if school enrollment status is not applicable). A single booster injection is sufficient to re-establish or maintain immunity in subjects whose records show that primary immunization has previously been completed. In children 7–12 years of age without records of prior diphtheria and tetanus immunization, it is advisable to perform a Schick test 6 to 12 months after the complete schedule (including the reinforcing dose—*c* below) has been given. This will detect the occasional child who may be less responsive to small doses of diphtheria toxoid than the normal adult, who should then receive an additional dose of the combined product.

b. Material. The preparation consists of a mixture of alum precipitated, aluminum phosphate absorbed or aluminum hydroxide adsorbed tetanus and purified diphtheria toxoids in such proportions that each 0.5 ml. dose contains 5–15 Lf of tetanus toxoid and only 1–2 Lf of diphtheria toxoid.

c. Methods of Immunization.

(1) Initial immunization consists of three intramuscular or subcutaneous injections, the first two doses of which will consist of 0.5 ml. of the combined toxoids per injection, and the third of 0.1 ml. The second injection should be given 1 to 2 months after the first and the third (reinforcing) injection 0.1 ml.) approximately 12 months after the second. For children under 12 years of age, 0.5 ml. should be given as the third dose to assure adequate immunity against diphtheria.

(2) To assure a circulating level of tetanus antitoxin adequate to protect a fighting man who might be in a situation where a booster dose of toxoid is not available at the time of injury, a booster dose of 0.1 ml.intramuscularly or subcutaneously should be given routinely every 6 years following completion of the initial series.

(3) This schedule will establish a long-lasting protective level of circulating tetanus antitoxin in the vast majority of subjects. However, to protect the occasional patient who does not maintain such a level and who is therefore subject to the risk of tetanus, it is still necessary to administer emergency booster ("wound booster") injections of 0.5 ml. of this product to all individuals who—

(*a*) have not received an injection of tetanus toxoid (either as such, or as DTP, T-d, etc.) within the preceding 12 months *and* who have either,

(*b*) incurred wounds or severe burns on the battlefield or are patients undergoing second operations or manipulations of old wounds.

(*c*) incurred puncture or lacerated wounds, severe burns or other conditions which might be complicated by the introduction of *Clostridium tetani* into the tissues. If, in the view of the medical officer, the patient's condition is such that an untoward reaction to either diphtheria or tetanus toxoid would be hazardous, a reduced dose of this product should be administered. The dose-response slope for a booster injection is quite flat so that a dose as small as 0.05 ml. will induce a significant response in patients with low antitoxin

titers. (For those personnel who have *not* received two or more doses of tetanus toxoid, passive immunity must be provided (para 21).)

d. Reactions. Erythema and induration at the site of injection occur occasionally and appear to be related to pre-existing immunity. These reactions are seldom severe; the incidence of severe reactions appears to be no more than 1 or 2 percent in individuals under 30 or 35 years of age and perhaps somewhat greater in those older. Urticarial and other allergic reactions occur rarely; they also are generally, though not invariably associated with already established hyperimmunity.

11. Poliovirus Vaccine, Live, Oral. *a. General.* Oral administration of live, attenuated polioviruses results in infection, with multiplication of these organisms in the gastrointestinal tract, leading to the development of a state of local resistance in the gastrointestinal tract. Serum antibody develops quickly as a sequel to this gastrointestinal infection. Repeated administration of the trivalent vaccine is necessary since immunizing infection with one strain may interfere with infection with other strains; on subsequent administrations, after the initial infection has cleared, the strains against which there is no immunity will multiply selectively. Upon subsequent exposure to naturally occurring polioviruses (wild viruses) this local resistance limits or prevents their intestinal multiplication and circulating antibody protects the central nervous system. Since serum antibody as well as gastrointestinal resistance develop rapidly, attenuated poliovirus vaccine may be used during an epidemic of poliomyelitis to prevent further spread of wild virus.

(1) The efficacy of this vaccine is evident from the polio experience in the United States. During 1967, only 41 cases of poliomyelitis were reported, in contrast to 6,000 to 8,000 in 1958 and 1959, prior to the wide scale use of this vaccine. The polio cases now occur in localized outbreaks predominantly among unimmunized children. This control has been achieved by an intensive immunization program of infants, children and adolescents. Because the risk of exposure within the continental United States has become small, routine poliomyelitis immunization is not considered necessary for adults. However, those who are employed in hospitals, medical laboratories, and sanitation facilities, as well as those who are at an increased risk because of contact with a known case or by travel to an endemic or epidemic area, should receive oral polio vaccine.

(2) Personnel who have received inactivated poliomyelitis (Salk vaccine) should be given live oral poliomyelitis vaccine in the same manner as those who have not.

b. Material. This vaccine consists of a mixture of the attenuated strains of Type 1, Type 2 and Type 3 poliomyelitis viruses, which are produced in cultures of monkey kidney cells. Since effectiveness depends on infectivity of the viruses, the vaccine should be kept frozen until use, used within 7 days after the bottle is entered, and not be refrozen. (Unentered bottles which have thawed accidentally may be refrozen under certain conditions (para 3*c*(2)).

c. Method of Vaccination. The vaccine is given by mouth according to the dosage instructions contained in the package. It may be added to a sugar cube, simple syrup or distilled water, or may be given with a sterile medicine dropper. It should not be given in, or followed immediately by, water or other beverage containing free chlorine or other halogen. Booster doses are given to children under 10; one dose is given 6 to 12 months after the basic series, and a second just before entering school. Adolescents may benefit from a booster dose 6 to 12 months after the basic series. Our present knowledge indicates that further boosters are not necessary; this, however, has not been established with certainty. Therefore, when faced with an epidemic or other unusual exposure, a single dose of trivalent vaccine may be given.

d. Reactions. These products have caused fewer adverse reactions than any other commonly used immunization. Neurological disease simulating paralytic poliomyelitis and occurring 4 to 30 days following a dose of oral vaccine has been reported in areas which were not recognized as epidemic. This has occurred at a rate below one per three million persons vaccinated but it is not known whether it is caused by the vaccine, wild poliovirus or other agents.

e. Contraindications and Precautions. It is not advisable to give the vaccine during a febrile illness. Pregnancy is not a contraindication, thus differing from most live viral vaccines. In most instances it has been found that this oral vaccine may be given, when necessary, at the same time as other attenuated vaccines, including oral adenovirus vaccine. Competition with some other enteroviruses is known to occur and for this reason administration during the summer season in temperate climates, or at any time in the tropics, may lead to such interference. This is far more likely to occur in children than in adults, for the incidence of such infections is much higher in the former, particularly the very young.

12. Typhus Vaccine. *a. General.* Circumstantial evidence gained in World War II and limited challenge studies in man suggest that an inactivated epidemic typhus vaccine can probably prevent an undetermined proportion of cases of epidemic typhus. It definitely reduces the severity and mortality of the disease. It offers little or no protection against murine typhus. A single dose of vaccine of adequate potency will elicit an antibody response in a high proportion of persons and will orient them promptly to a single booster dose after an appropriate interval, usually considered to be a minimum of 6 to 9 months. Antibody response to booster doses given less than 6 months after the primary dose may be irregular. However, once immunologically oriented with typhus vaccine, a person may respond promptly to a single booster given as long as 15 years after the primary immunization. A second dose given shortly after a booster often fails to increase antibody titer significantly. Unfortunately, problems have developed in the manufacture of typhus vaccine, so that certain lots acceptable by laboratory criteria are ineffective in eliciting an antibody response in man. Until this paradox is resolved, the killed typhus vaccine is unavailable for routine use. An attenuated strain of *Rickettsia prowazekii* (strain E) is under laboratory study for effectiveness and acceptability; preliminary results suggest that this might afford some limited or irregular, protection against murine typhus as well, and that a single dose will confer protection for a prolonged period. Immunization against epidemic, louse-borne typhus should be considered not as a substitute for, but as an adjunct to louse-control measures.

b. Material. Typhus vaccine contains killed epidemic typhus rickettsiae grown in egg yolk sacs.

c. Method of Vaccination. Primary immunization (basic series) is accomplished by administration of the dosage schedule stated in the package insert or appropriate directives, by syringe and needle subcutaneously or intramuscularly or by jet gun. When directed by an area commander, booster doses, consisting of 0.5 ml. vaccine given by the same routes, may be required in areas where a typhus hazard is considered to exist. Because potency tests and minimum requirements for the vaccine are currently under intensive reevaluation, changes in dose or regimen may be made from time to time.

d. Reactions.

(1) Because the vaccine is produced from the infected yolk sacs of hen's eggs, the vaccine should not be administered to persons with a history of allergy to eggs or chickens without appropriate precautions (para 4*b*(2)).

(2) Typhus rickettsiae contain endotoxin-like substances. Occasionally, local and/or febrile systemic reactions similar to those elicited by typhoid vaccine may be encountered.

(3) Delayed type hypersensitivity to typhus antigens may develop following recovery from typhus fever or after repeated typhus vaccination. On occasion, therefore, exaggerated local and systemic reactions may be encountered when vaccine is administered to a sensitized person.

13. Yellow Fever Vaccine. *a. General.* Vaccination with this live attenuated virus vaccine is considered to provide almost absolute immunity lasting at least 10 years and probably much longer. A subclinical infection is produced by the attenuated strain, not infrequently associated with a transient viremia about a week after injection. The strain of virus in use in the United States is not neurotropic.

b. Material. Yellow fever vaccine consists of a special strain (17D) of *living* yellow fever virus which had been attenuated through culture in *chick embryos* so that it produces only subclinical infection in man with subsequent immunity. The vaccine is prepared from chick embryo material, is freeze-dried, and stored and shipped at a temperature not higher than 0°C. (32° F.) (para 3*c*(1)). The reconstituting fluid (physiological saline without preservative) is stored separately at above freezing temperatures.

c. Method of Vaccination.

(1) For use, the vaccine is reconstituted strictly according to the manufacturer's instructions (these are packed with the ampule containing the vaccine). This results in a 1:10 dilution of the original concentrated vaccine. Any reconstituted vaccine remaining at the end of one hour should be discarded.

(2) The vaccinating dose for all ages is one subcutaneous or intramuscular injection of 0.5 ml. of vaccine. If a jet injector is used, and this has contained a disinfectant or other virucidal substance, the injector should be purged by ejecting 10 to 15 ml. of sterile saline before placing the vaccine bottle on the injector (para 5*b*). Reimmunization is accomplished every 10 years and the dose is the same as the original vaccinating dose.

d. Reactions.

(1) About 5 percent of the individuals may experience a mild febrile reaction about 5 to 7

days after receiving yellow fever vaccine. Extensive experience during World War II has established that there is no strong objection to the simultaneous administration of yellow fever vaccine and other vaccines or toxoids. However, an exaggerated reaction to typhoid or influenza vaccine may result if they are administered to individuals who are actually experiencing a febrile reaction to a previously administered dose of yellow fever vaccine. Therefore, the administration of such vaccines within a 5 to 7 day period following yellow fever vaccination should be avoided, when practicable.

(2) Human serum is no longer used as a stabilizer for the vaccine; hence, hepatitis is not a complication of yellow fever vaccination. A history of jaundice is not a contraindication to immunization or to the administration of booster doses.

(3) Encephalopathy is a very rare complication of yellow fever vaccination. With the exception of a single fatal case in a 3-year-old child, all have occurred in infants under 7 months of age and all of those recovered without sequelae.

e. Contraindications and Precautions (Para 6). Concurrent administration of smallpox, measles and yellow fever vaccines in different sites produce seroconversion rates comparable to those vaccines when given singly. Injection of a mixture of these vaccines results in a significantly lower percentage developing antibodies against yellow fever. Because of the egg origin of yellow fever vaccine, the vaccine should never be administered to individuals with a history of allergy to eggs or chickens without appropriate precautions (para *4b*). Vaccination of infants is only performed when there is actual risk of exposure. Yellow fever immunization evokes circulating interferon which may prevent another live virus vaccine from establishing immunity.

14. Influenza Vaccine. *a. General.* Because of the year-to-year variation in the strains of influenza virus isolated from patients and variation in the immunity of the population against these strains, the composition of influenza vaccine must be changed periodically. Details regarding its manner of use cannot be promulgated either far in advance or on a routine basis; in some years, a broad base of immunity against many strains may be sought together with a high level of immunity against the more common strains; in other years, specific immunity against an epidemic strain is desired. A fairly high degree of protection against strains of influenza virus antigenically similar to the strains used in the vaccine is provided for 12 months or longer by vaccination. Little or no protection may be provided against less closely related strains.

b. Material. Influenza vaccine is a killed suspension of one or more strains each of types A and B influenza virus obtained from the allantoic fluid of inoculated embryonated eggs. The finished vaccine is subjected to variable degrees of purification, so that it varies from essentially a crude harvest to a highly purified viral fraction or highly purified viral subunits. For initial immunization, the vaccine will usually contain a wide spectrum of strains in order to provide as broad an antigenic orientation as possible. For booster doses polyvalent or monovalent vaccines may be prescribed, depending on prevalent virus strain patterns.

c. Method of Vaccination. The dose of usual aqueous vaccine is 1 ml. administered subcutaneously or intramuscularly. Care must be taken to insure that the vaccine is not given to individuals allergic to chicken or eggs; persons who eat eggs or egg products can receive this vaccine with impunity (para *4b*(2)).

d. Reactions. Local or systemic toxic reactions similar to those observed following the administration of typhoid vaccine may occur following influenza vaccination. They can be readily controlled with aspirin.

15. Cholera Vaccine. *a. General.* Field studies have shown that the incidence of cholera is significantly lower among those who have received this vaccine and this protection lasts for 6 months or longer. Protection is afforded against disease caused by the "El Tor" type of organisms as well as against disease caused by the classical vibrios. However, vaccination does not prevent inapparent cholera infection. Since occasional convalescent patients may harbor vibrios for weeks, months or even years, with vibrios demonstrable only by duodenal drainage or by magnesium sulfate purges, these apparently healthy persons can become sources of infection should the individual develop intercurrent diarrhea. Therefore, vaccination is definitely secondary in value to sanitary measures to prevent contamination of food and water and for the safe disposal of human wastes. Reliance must never be placed on vaccination alone.

b. Material. Cholera vaccine consists of a suspension of 8,000 million killed cholera vibrios (*Vibrio cholerae*) per ml., containing equal numbers of the Inaba and Ogawa serotypes.

c. Method of Vaccination. The basic series consists of two subcutaneous or intramuscular injec-

tions, the first of 0.5 ml. and the second of 1.0 ml., given by jet injector or by syringe and needle. The interval between the two doses has been 4 weeks; current studies indicate, however, that in adults antibody levels as high or higher can be achieved when the interval is only 1 week. Reimmunization with 0.5 ml. may be required every 6 months in areas where cholera is epidemic or highly endemic and personnel may be exposed to infection. For international quarantine purposes, the vaccination certificate is valid from 6 days after immunization for 6 months and for 6 months after a booster dose, if this is given within 6 months. If more than 6 months have elapsed, the vaccination certificate is not valid for travel into nonendemic areas until 6 days have elapsed.

d. Reactions. Local or systemic toxic reactions may follow the administration of cholera vaccine, especially on reimmunization. Rarely, with some lots of vaccine, sterile abscesses may occur; these may be tapped but should not be incised.

16. Plague Vaccine. *a. General.* While the effectiveness of plague vaccine has never been accurately determined, immunization is known to reduce the incidence and severity of insect-borne disease, the bubonic form. The greatly increased resistance which follows booster inoculations justifies the administration of the basic immunization series to most military personnel since there are so many areas in the world, i.e., Western United States, South America, Africa and Asia, including Viet Nam, where the individual in military operations may come into frequent and regular contact with infected wild rodents. However, sensitization to the vaccine results in increased reactivity with subsequent doses. For this reason, the dose for booster injections is reduced in volume and only given intramuscularly. Boosters are only given to those residing in known plague endemic areas, not more often than every 6 months. Once a basic series has been given, it should not be repeated regardless of the length of time since the completion of the basic series. While vaccine is assumed to provide some protection against bubonic disease, it is not known whether it affords any protection against pneumonic disease; if exposed to pneumonic plague, vaccinated persons should be given daily adequate doses of tetracycline or suitable sulfonamide over a 6-day period.

b. Material. Plague vaccine contains 2,000 million formaldehyde-killed bacilli (*Pasteurella pestis*) per ml., preserved with 0.5 percent phenol. The E medium currently used is one which is free of blood-group antigens.

c. Method of Immunization. Basic immunization against plague consists of one intramuscular injection by syringe and needle or jet injection of 1.0 ml. of vaccine followed in three months by an intramuscular injection of 0.2 ml. (by syringe and needle only). No further boosters are administered unless the individual is actually residing in a known plague endemic area, presently considered to be Laos, Cambodia and Viet Nam. While the administration of 1.2 ml. of vaccine constitutes the complete basic series, the administration of the first 1.0 ml. dose is considered adequate protection to permit travel to a plague area where the remaining dose may be given. Booster injections will be 0.2 ml. administered intramuscularly, by syringe and needle only at 6-month intervals; the first booster will be given no sooner than 6 months following the second injection of the basic series. Although plague is an internationally quarantinable disease, vaccination is not a condition for admission to any country. Appropriately reduced doses are administered to children.

d. Reactions. Primary immunization may result in general malaise, headache, local erythema and induration, mild lymphadenopathy and hyperpyrexia in about 10 percent of recipients. Reactions are more intense with booster injections. Local reactions are particularly intense and are minimized by the intramuscular deposition of the booster dose. It is for this reason that booster doses are not jet injected.

SECTION III

SPECIAL IMMUNIZATIONS

17. Adenovirus Vaccine. *a. General.*

(1) The use of these vaccines can be authorized solely by the appropriate Surgeon General.

(2) Living attenuated adenovirus type 4 vaccine, given orally, has been shown in field trials to be safe and between 95 and 99 percent effective against type 4 disease, but does not protect against disease caused by other adenovirus types. Specific protection is induced by asymptomatic gastrointestinal infection with the vaccine virus. The vaccine virus has been partially attenuated by serial passage in human diploid cells, is not oncogenic for newborn hamsters, and is free of simian and adenovirus associated viruses. Immunized persons shed vaccine virus in their stools up to 21 days following ingestion. There is no evidence of significant transmission of this shed virus among recruits. Living vaccines for other adenovirus types (7 and 21) are currently under investigation.

b. Material. Oral vaccine is supplied as enteric coated tablets containing approximately 10^6 tissue culture infectious doses of virus. Vaccine is stable at 4°C. for at least 24 months.

c. Method of Vaccination. For maximal effectiveness, oral vaccine should be given as soon as possible after the recruit's arrival on the training center. One tablet is sufficient to induce type specific immunity. Vaccine effect in epidemics is noted approximately 14 days after administration. Oral immunization with adenovirus vaccine does not interfere with simultaneous oral poliovirus immunization or vice versa. Similarly, neither interference nor exaltation is observed when both types 4 and 7 virus in recommended dosage is administered simultaneously in persons susceptible to both infections. Both type 4 and type 7 virus vaccines may be given simultaneously with other required immunizations.

d. Reactions. Oral immunization and intestinal propagation of viruses are not associated with reactions.

e. Contraindications and Precautions. See paragraph 6.

18. Rabies Vaccines and Antirabies Serum. *a. General.* These products differ from most agents employed for inducing immunity in that they are usually used after exposure to the disease has occurred. Since control of the wild animal reservoirs of rabies is not feasible in most areas of the world, it is imperative that all personnel involved in the management of those who might be exposed to rabies be thoroughly familiar with the use of the rabies vaccines and antirabies serum. Primary emphasis is placed on the treatment of the bite wound; rabies vaccine has been used for postexposure prophylaxis for 85 years; the addition of hyperimmune serum has greatly improved the effectiveness of prophylaxis.

b. Material. There are two rabies vaccines currently available for the Armed Services for prevention of human rabies.

(1) Rabies Vaccine, USP, Duck Embryo, is an inactivated preparation produced in embryonic duck tissue. This vaccine is now more commonly used in the Armed Forces than the Semple vaccine and should be used in any individual known or believed to be sensitive to vaccine containing nerve tissue.

(2) Rabies Vaccine, USP, is a preparation of infected central nervous system tissue, commonly a fluid, phenol-killed suspension of virus in rabbit brain (referred to as Semple vaccine). Use of this vaccine is associated with a neuroparalytic type of reaction in approximately one of every 3,000 individuals who have received it.

(3) Antirabies serum is hyperimmune horse serum and, even though fractionated and concentrated, may produce adverse reactions in approximately 20 percent of the recipients (para 4*b*(2), (2)(*e*), and (4)). Most serious sensitivity reactions may be avoided if a careful history for previous allergies is taken and routine sensitivity testing is performed. When sensitivity has been demonstrated and the exposure is such that the use of antirabies serum is indicated, desensitization should be accomplished. The incidence and severity of sensitivity reactions may be reduced by concurrent administration of antihistaminics; however, their use will not obviate the necessity for the precautions outlined in paragraph 4.

(4) Antirabies serum of human origin is under investigation. Preliminary data indicate that this does not interfere with active immunity induced by a sufficiently potent vaccine.

c. Methods of Immunization.

(1) *Indications for Rabies treatment.* The determination of whether to administer vaccine and antirabies serum should be made only after examination of the patient, examination of the animal, if possible, and careful evaluation of the circumstances. It is very helpful to establish and use a "rabies board," composed of carefully selected physicians and a veterinarian. (Army: See AR 40–5.) The following should be borne in mind—human rabies is almost invariably fatal, but not all persons bitten or scratched by a rabid animal develop rabies. Clothing offers considerable protection, apparently by the mechanical removal of the saliva from the animal's teeth. Deep puncture, lacerated or extensive, chewed wounds are more likely to permit the virus to come into direct contact with nerve tissue and are particularly dangerous. Rabies can be acquired via the gastrointestinal tract from consumption of meat and/or milk from rabid animals. In man, the average incubation period is 42 days but may be as short as 10 days or as long as 9 months, depending on wound severity and distance from the brain. Appendix B is an adaptation of the recommendations of the World Health Organization Expert Committee on Rabies (WHO Technical Report Series No. 321, 1966, obtainable through the WHO Book Service, American Public Health Association, 1740 Broadway, New York, New York 10019). This table, in conjunction with the detailed history of the circumstances of exposure, can assist the "rabies board" in determining the course to be followed.

(*a*) *Rabies prophylaxis, post exposure* (*app B*).

1. Local treatment of bite wound. All bite wounds should be cleansed thoroughly as soon as possible after the bite. This is probably the most important single procedure in preventing rabies. Mechanical cleaning and flushing of the wound with soapy water without traumatizing tissue is the basic procedure, followed by application of 1 percent benzalkonium chloride *after all traces of soap* have been removed. Topical application of antirabies serum and infiltration of serum around the wound is important to neutralize the virus whenever serum prophylaxis is indicated (see below).

2. The WHO Expert Committee on Rabies recommends that the *best* specific treatment available for the postexposure prophylaxis of rabies in man is combined antirabies serum or its globulin fraction and the vaccine. This is especially true for severe exposures, bites of the head and neck and bites from wild animals. Furthermore, the WHO Committee states that "although experience indicates that vaccine alone is sufficient for mild exposures, there is no doubt that even with mild exposure, the combined serum-vaccine treatment will give the best protection." The individual physician with the advice of the "rabies board" must make the clinical decision on the use of hyperimmune serum in relation to needed protection and risk of creating hypersensitization. Protection against rabies depends upon active immunization, with the production of antibodies, in response to an inactivated vaccine, but several days elapse after injections are started before antibodies can be detected in the serum. During this period the virus inoculated by the bite of the animal may gain entry into nerves. To provide an immediate barrier to the virus, passive immunological protection may be provided with antirabies serum. This temporarily slows down or halts the spread of the virus, allowing time for active immunity to develop. Serum with a high antibody content (hyperimmune serum) *is injected preferably within 24 hours after the bite and after appropriate skin testing* (*para 4b* (2)(*d*)). A portion of the serum should be injected directly into the injured tissues. *The vaccine therapy is started concurrently.*

3. Special conditions warranting treatment modifications. In areas where rabies is known to be enzootic and an animal has severely bitten an individual about the face, immediate initiation of treatment, even though the animal at the time of exposure appears healthy, should be considered. Under certain conditions other modifications might be adopted. For example, local treatment of the wound, a single dose of serum and three daily doses of vaccine may be given. If the animal stays healthy for 10 days, no further treatment is necessary. Another example of a local situation in which a modified interpretation of these recommendations may be indicated is that of a rabies-free area (for example, a rabies-free country or state of the United States). In such localities, no specific antirabies treatment may be justified; however, the biting animal should be kept under observation for 10 days. Unless rabies is known to exist in the species, bites (particularly provoked bites) by small wild rodents such as mice and rats may require only local wound treatment and reassurance to the patient. Specific antirabies therapy should be considered, but in most cases is not indicated, even if the wild rodent is not apprehended.

(*b*) *Rabies immunization, pre-exposure.*

1. Immunization phase. Particular groups of individuals, such as veterinarians, dog handlers, members of research field teams handling wild animals and laboratory workers in highly endemic areas have increased exposure to rabies. Area surgeons or medical commanders may recommend, with the approval of the appropriate Surgeon General, pre-exposure immunization to personnel stationed in or visiting areas where rabies is highly endemic. To vaccinate these personnel each time they are exposed would increase the possibility of their having sensitivity reactions to the vaccine. A pre-exposure immunization schedule using duck embryo vaccine, consisting of two subcutaneous 1 ml. doses one month apart, followed by a booster dose administered 6 to 8 months after the second dose of vaccine, is recommended. If feasible, 1 month after the booster dose a serum sample should be tested for antirabies antibodies. Not all vaccinated individuals respond readily with detectable antibodies; therefore, *booster doses should be repeated until antibody is detectable.* Subsequently, single booster doses at one to two year intervals are recommended as long as the person remains at risk.

2. Action in case of exposure to rabies. When a vaccinated person has been shown to have developed rabies antibodies and is subsequently exposed to rabies in the next 2 years, a single booster dose of vaccine (and no antiserum) is recommended in the case of a mild exposure. After a severe exposure five daily doses of vaccine plus a booster dose 20 days later are indicated. If more than 2 years have elapsed since immunization or *if it is not known whether an exposed person had developed antibodies,* full postexposure treatment should be given.

(2) *Technique of administration.* Antirabies serum, in a total dose of 40 International Units per kg. of body weight is given intramuscularly; part is infiltrated into the tissues around the bite. This is followed by a course of not less than 21 daily subcutaneous doses of vaccine, unless the animal is proven nonrabid after 10 days' observation. *Two supplemental doses of vaccine, preferably duck embryo vaccine, should be administered at 10 days and between 20 and 40 days after completion of the course of vaccinations.* Manufacturer's recommendations, packaged with the vaccine, should be followed. The abdomen is usually used because this will provide sufficient space to avoid two injections at one site. A careful record of the exact site of each injection should be maintained during treatment to reduce discomfort to the patient.

(3) *Revaccination.* An individual who has received complete antirabies treatment and is subsequently re-exposed to rabies, should be given either a single booster dose, 5 daily doses, or full postexposure treatment depending on severity of bite and upon the elapsed time since previous inoculation.

d. Reactions.

(1) Local reactions usually are insignificant and consist of redness and induration, usually at the site of previous injections. This is not a contraindication to continuation of vaccination. Occasionally severe local reactions may occur and the decision about continuation of treatment will require a most careful evaluation.

(2) One individual in approximately 3,000 has a neuroparalytic reaction to the administration of nerve tissue vaccine. This reaction is believed to be the result of a sensitivity reaction to the neural tissue component of the vaccine. It may take the form of an ascending paralysis, paraplegia due to myelitis or localized paralysis. The onset is usually more than 1 week after the beginning of treatment. If such a reaction occurs or premonitory symptoms arouse suspicion (severe headache, fever, nausea, urticaria, generalized lymphadenopathy), vaccination should be terminated immediately. If, in view of the nature of the exposure and duration of treatment, it is felt that sufficient immunity has not been attained, treatment should be continued with duck embryo vaccine. With this latter product, the most important serious reaction may be the allergic response in a person sensitive to duck eggs. Such individuals should be given duck embryo vaccine with extreme care. In extremely rare instances even duck embryo vaccine may cause a neuroparalytic accident.

19. Measles Vaccine, Live Attenuated. *a. General.* Live attenuated measles-virus vaccines produce an inapparent or mild infection which is noncommunicable and is followed by immunity for at least 10 years. The available evidence indicates a single inoculation will generally be followed by permanent immunity; rare cases of typical measles have been reported in children immunized several years earlier. Experience with approximately 30 million doses administered in the United States between 1963 and 1968 indicates that the vaccines are safe and highly effective; measles now occurs predominantly in communities which have failed to immunize their children.

b. Material. Four types of live measles virus vaccines have been licensed for use in the United

States. Each manufacturer employs a derivative of the Edmonston strain of attenuated measles virus; some are at lower passage levels, having the general characteristics of the Edmonston B-level experimental vaccine originally described by Enders and Katz. Most vaccines of this type are propagated on chick embryo cell cultures; one is produced on dog kidney cell cultures. These lower passage vaccines are commonly associated with fever and rash, so that some manufacturers recommend that immune serum globulin (human) be given concurrently to reduce the frequency and intensity of these reactions. More attenuation is achieved by additional passages in chick embryo cell systems; these more attenuated vaccines (Schwarz and Moraten strains) tend to evoke somewhat lower levels of antibody but reactions are reduced so that immune serum globulin is not used.

c. Method of Vaccination.

(1) Live measles vaccine should be given to all infants and children over 12 months of age if they have not had measles; it is effective if given before or on the day of exposure to natural measles. When administered after the day of exposure, limited studies indicate that protection is not conferred nor are adverse effects induced. Passive protection (para 26) may be indicated under certain circumstances. Immunization is especially important for children with chronic diseases, such as tuberculosis, cystic fibrosis, other pulmonary diseases, congenital heart disease and malnutrition. Vaccination of adults is rarely necessary because nearly all individuals are immune by age 18. Susceptible adults may be vaccinated; the reactions are essentially the same as those in children.

(2) Measles vaccine has been given simultaneously (but at different sites) with smallpox and yellow fever vaccines with no obvious untoward effect and with evidence of an antibody response to the three live virus vaccines. Experimental trials with live measles-mumps and measles-mumps-rubella combination vaccines have also been successful (para 6).

d. Reactions.

(1) Fever may occur approximately 5 to 10 days after vaccination, even when gamma globulin has been administered concurrently in the other extremity. In spite of high fevers in about 15 percent of vaccinees, there is minimal toxicity and little discomfort. A maculopapular rash may occur. Most children have no reactions.

(2) Administration of live vaccine to those who have previously received inactivated measles vaccine has induced a local reaction at the site of injection with erythema, heat, tenderness, swelling and localized vesicular or hemorrhagic rash and occasionally with fever, malaise and regional lymphadenopathy. On the other hand, exposure to natural measles a few years after immunization with the inactivated vaccine has resulted in a severe illness characterized by high fever, toxicity, a petechial, vesicular and urticarial rash, edema and pneumonia. *Since the reactions to the attenuated vaccine are of less importance than those following natural exposure, live vaccine should be given as soon as possible to all who have been immunized with only inactivated vaccine, warning parents of the possible local and systemic reactions.* Children with contraindications to live vaccine should be protected by immune serum globulin on exposure to measles.

e. Contraindications and Precautions (para 6). Children with tuberculosis should be under specific treatment before receiving measles vaccine. Vaccination should be postponed until recovery from a febrile illness, if present. Vaccination should be deferred for three months after administration of gamma globulin. Chick embryo vaccines should not be given to children hypersensitive to egg proteins and those sensitive to dog dander should not receive canine tissue culture

20. Tetanus Toxoid. This product is not to be used routinely in immunization against tetanus, as it has been replaced by tetanus and diphtheria toxoids combined, precipitated, adsorbed (for adult use.) It has been used extensively in the past for emergency booster injections in patients who, it was thought, could not tolerate the combined product presumably because of sensitivity to diphtheria toxoid. However, many reactors to the combined product proved to be hyperreactive to the tetanus component; their situation is best handled by administering a small dose (0.05 ml to 0.1 ml) of the combined product. Formerly, a fluid product was provided, but subsequent studies have shown that the antitoxic response to an adsorbed toxoid is as rapid or more rapid than to a fluid toxoid, while products containing aluminum salt adjuvants produce fewer adverse reactions. Because of this and because of the consistently higher titer they evoke, products containing alum adjuvants are the agents of choice for all primary and booster injections.

21. Tetanus Immune Globulin (Human) and Tetanus Antitoxin. *a. General.* When the status of previous immunization is such that there is no assurance of circulating antibody at the time an

injury occurs, passive protection must be provided by the use of Tetanus Immune Globulin (Human)—so-called "Human Tetanus Antitoxin" (TIG)—which has replaced antitoxin prepared in animals (TAT) as the standard product for military use. The indications for the administration of either product are limited to—

(1) The treatment of clinical tetanus.

(2) The prophylaxis of tetanus in individuals who have suffered injury which might give rise to tetanus and who have not received the first two doses of tetanus toxoid.

When the human product is used, protective antibody levels persist for a much longer period of time since antibodies directed against it are not usually formed as occurs with a foreign protein; this virtually eliminates danger of anaphylactic reactions intradermal testing is not done (gamma globulin normally elicits a reaction on intradermal injection).

b. Material. Globulin, tetanus immune (human) is the globulin fraction of plasma obtained from humans with high tetanus antitoxin titers. Tetanus antitoxin is obtained from hyper-immunized horses (or cows), usually fractionated and concentrated and often enzyme treated to reduce sensitivity reactions.

c. Method of Use (Prophylactic).

(1) *Tetanus Immune Globulin (Human).* 250 units are given intramuscularly; for crushing wounds or extensive burns, 500 units should be given. When specific prophylaxis is given more than one day after injury, the dose should be increased 2 to 4 times or more, depending on the length of delay and wound complication.

(2) *Tetanus antitoxin.* 5,000 units IM (or SC if given in divided doses). In case of delay, see (1) above.

(3) *Combined active-passive immunization.* All individuals requiring passive prophylaxis with Tetanus Immune Globulin (Human) or Tetanus Antitoxin have by definition received less than two injections of any form of tetanus toxoid. If such a patient has had no previous injection or only one previous injection containing tetanus toxoid, a standard dose of the scheduled product (DPT if under 7 years, T-d if 7 years or older) should be administered simultaneously with the passive prophylaxis but in separate syringe and at a separate site.

d. Reactions.

(1) Tetanus Immune Globulin (Human) is not to be administered intravenously, since the usual partially aggregated material may produce a severe shock-like reaction. Experimental preparations which can be given intravenously without adverse reaction are under study.

(2) Tetanus Antitoxin will only be used when Tetanus Immune Globulin is not available. Because of the relatively high frequency of serious sensitivity reactions experienced with tetanus antitoxin containing horse serum (para 4), the physician must very carefully evaluate the situation before administering antitoxin. The dependability of the history of prior immunization and the nature of the injury must be considered. A careful history of allergic sensitivity and of prior injections of horse serum must be taken. In addition, regardless of the previous history of not having received tetanus antitoxin, any person for whom the use of this material is considered must be skin tested by the intradermal injection of appropriate dilutions. When the skin test or history indicates that a state of hypersensitivity to equine TAT exists, and when TIG cannot be obtained, antitoxin prepared in another species (e.g., bovine) may be substituted if available; the same precautions regarding sensitivity are required as with the standard tetanus antitoxin of equine origin. If only equine antitoxin is available, it may be administered in fractional doses (commonly but probably incorrectly referred to as "desensitization"), starting with an injection of 0.001 ml (0.1 ml of 1:100 diluent). If a severe reaction to the skin test or the fractional dose (para 4*d*) is encountered, penicillin (procaine penicillin, 600,000 units daily for 10 days) or broad-spectrum antibiotics, oxytetracycline or erythromycin (1.0 gram daily in divided doses for 10 days) may be of some value in persons if given early after injury. The use of penicillin or other antibiotics to the exclusion of tetanus antitoxin and adequate surgical care of the injury is not recommended under any circumstances; every effort should be made to obtain tetanus immune globulin (human).

22. Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Adsorbed. This is a *pediatric* preparation for immunization and reimmunization of children under 7 years of age. It contains aluminum salts ("alum"). Immunization with this product is accomplished by the administration of three intramuscular injections, normally 0.5 ml each (see manufacturer's instructions) at approximately 1 to 2 month intervals. It is recommended that this immunization be initiated at 2 to 3 months of age, that a reinforcing dose be given at 16 to 18 months of age and that a booster injection be given at 4 to 6 years of age, preferably at the time when the child first enters a school or kindergarten. Use

of this product in children over 6 years of age is generally not indicated or recommended, when scheduling permits, it is preferable not to give it concurrently with a live virus vaccine.

23. Mumps Vaccine. *a. General.*

(1) Prevention of mumps has been attempted by—

(*a*) Administration of hyperimmune gamma globulin,

(*b*) Vaccination with inactivated vaccine, and

(*c*) Vaccination with live attenuated virus vaccines. Results of passive protection with gamma globulin have not been sufficiently regular to justify its use and the protection afforded is transitory. Vaccination with inactivated mumps virus vaccines provides protection in 80 to 90 percent of inoculated individuals but the induced immunity is only shortlived and cannot be expected to last for more than about 1 year. This type of vaccine should only be used if live attenuated mumps virus vaccine is not available. Live attenuated mumps virus vaccine induces immunity in 90 to 100 percent of the vaccinees and resistance can be expected to last for prolonged periods of time. At present, vaccinated individuals have only been observed for 4 years. There is no evidence that either inactivated or live attenuated vaccines will protect against disease if given to already infected individuals (there is no contraindication to the administration of inactivated or live vaccine during the incubation period), but vaccination of a population at the onset of an epidemic will abort the outbreak and no further cases should occur 3 to 4 weeks after vaccination.

(2) The use of live attenuated mumps vaccine is not routinely recommended for military personnel but should be limited to use in certain outbreaks of mumps. Under such circumstances the vaccine should be given to all individuals, including dependents, who do not have a history of mumps. The vaccine may be used at any age from 12 months; it should not be administered to children less than 12 months because of possible interference by persisting maternal immunity. It is of particular value in children approaching puberty, in adolescents and in adults, especially males. The most valuable measure of immunity is a history of clinical disease; for those with a negative history, immunity can be determined by an evaluation of the presence of circulating antibodies. Antibody testing is indicated only under special circumstances and vaccination should not be postponed pending the results of these tests.

b. Material.

(1) *Mumps, vaccine, live attenuated.* Virus grown in chick embryo fibroblast tissue culture is supplied as freeze-dried material, and should be stored at 2°C. through 8°C. *Reconstituted vaccine should be used immediately, or within 8 hours if held at 2°C. through 8°C. Reconstituted vaccine not used within this time limit should be discarded.*

(2) *Mumps vaccine, inactivated.* Virus grown in the allantoic cavity of embryonated hen's eggs, partially purified and inactivated with formalin, is supplied in fluid form and should be stored at 4°C. (refrigerator temperature).

c. Method of Vaccination.

(1) *Live attenuated vaccine.* One dose of 0.5 ml. (see manufacturer's instructions) should be given subcutaneously. Vaccine may be administered by needle and syringe or by jet injector.

(2) *Inactivated vaccine.* Two doses of 1 ml each should be given 1 to 3 weeks apart intramuscularly or subcutaneously. A booster dose (1 ml as before) is recommended 6 months to a year later. Live attenuated vaccine should be used for the booster inoculation if available.

d. Reactions. Only rare reactions have been noted after this vaccine. Local erythema and induration have occurred rarely; temperature patterns are similar to that in unvaccinated controls.

e. Contraindications and Precautions. This living vaccine should not be given to anyone with an acute febrile illness or a possibly impaired immunological response (para 6). Individuals who cannot eat eggs or egg products, or who report a known allergy to egg protein should not be vaccinated. While the vaccine only contains small amounts of antibiotics, it should not be given to neomycin-sensitive individuals.

24. Rocky Mountain Spotted Fever Vaccine. *a. General.* Vaccination with presently available products provides little, if any, protection against Rocky Mountain Spotted Fever but may diminish the severity of the disease. Therefore, chief reliance for prevention should be based on avoidance of ticks or frequent inspection and prompt removal when avoidance is not possible. Infected ticks do not usually transmit the disease for some 4 to 6 hours after first contact with an individual. Rocky Mountain Spotted Fever vaccine is not administered routinely in the Armed Forces. It may be used with the approval of the appropriate Surgeon General for personnel who must spend considerable time in tick-infested areas

where Rocky Mountain Spotted Fever is present. The vaccine can only be effective when used prior to exposure. Since it has not been shown to afford significant protection, greatest reliance must be placed on *early* diagnosis and treatment if serious complications or fatalities are to be avoided.

b. Material. The vaccine consists of a suspension of killed Rocky Mountain Spotted Fever rickettsiae (*R. rickettsii*) grown in *egg yolk sacs.*

c. Method of Vaccination. The basic series consists of three subcutaneous 1 ml doses given at intervals of approximately 7 days or as specified on the container. Revaccination may be accomplished by administering 0.5 ml subcutaneously annually prior to exposure.

d. Reactions. As with other egg-grown vaccines, this vaccine should not be administered to persons who are intolerant of eggs or who have known sensitivity to eggs. Occasionally local and/or febrile systemic reactions similar to those elicited by typhoid vaccine may occur.

25. **Rubella Vaccine.** *a. General.* The live, attenuated rubella virus vaccine appears to be a highly effective immunizing agent and the first suitable method of controlling rubella. Rubella is generally a mild illness, but if the infection is acquired by a woman in the early months of pregnancy, it poses a direct hazard to the fetus. Preventing infection of the fetus is the principal objective of rubella control. This can best be achieved by eliminating the transmission of virus among children, who are the major source of infection for susceptible pregnant women. Furthermore, the live, attenuated rubella virus vaccine is safe and protective for children, but not for pregnant women because of an undetermined risk of the vaccine virus for the fetus.

b. Rubella Immunity. Immunity following rubella appears to be long lasting, even after mild illness or clinically inapparent infection. The only reliable evidence of immunity is a positive serological test. However, because of the variation among reagents and technical procedures, results of serological tests should be accepted only from laboratories of recognized competency that regularly perform these tests. At the present time, the hemagglutination-inhibition (HI) antibody determination is particularly useful for evaluating immunity. It is a rapid and sensitive procedure. The complement fixation (CF) and other serological tests are less useful.

c. Material.

(1) Live rubella virus vaccine is prepared in cell culture of avian or mammalian tissues. It is administered as a single subcutaneous injection. Although vaccinees shed virus from the pharynx at times for 2 or more weeks after vaccination, there is no clear evidence of communicability. Approximately 95 percent of susceptible vaccinees develop antibodies, but titers are lower than those observed following natural rubella infection. Recent investigations have shown that vaccination affords protection against illness following either natural exposure or artificial challenge. Antibody levels have declined very little during the 3-year period of observation of children who were among the first to be immunized with rubella vaccine. Long-term protection is likely, but its exact duration can be established only by continued observation.

(2) More than 30,000 susceptible children have received live rubella virus vaccine in field investigations with almost no untoward reactions. Only rarely has transient arthralgia or evanescent rash been reported in children. Many susceptible women have had lymphadenopathy, arthralgia, and transient arthritis beginning 2 to 4 weeks after vaccination; however, fever, rash, and other features of naturally acquired rubella have occurred less commonly. Not enough susceptible men have been vaccinated to show whether they experience comparable reactions as frequently.

d. Method of Vaccination.

(1) Live rubella virus vaccine is recommended for boys and girls between the age of 1 year and puberty. Vaccine should not be administered to infants less than 1 year old because of possible interference from persisting maternal rubella antibody. Children in kindergarten and the early grades of elementary school deserve initial priority for vaccination because they are commonly the major source of virus dissemination in the community. A history of rubella illness is usually not reliable enough to exclude children for immunization. *Pregnant women should not be given live rubella virus vaccine.* It is not known to what extent infection of the fetus with attenuated virus might take place following vaccination, or whether damage to the fetus could result. Therefore, routine immunization of adolescent girls and adult women should not be undertaken because of the danger of inadvertently administering vaccine before pregnancy becomes evident.

(2) Women of child-bearing age may be considered for vaccination only when the possibility of pregnancy in the following 2 months is essen-

tially nil; each case must be considered individually. This cautious approach to vaccinating postpubertal females is indicated for two reasons: First, because of the theoretical risk of vaccination in pregnancy and second, because significant congenital anomalies occur regularly in approximately 3 percent of all births, and their fortuitous appearance after vaccine had been given during pregnancy could lead to serious misinterpretation. If vaccination of a woman of child-bearing age is contemplated, the following steps are indicated.

(*a*) Optimally, the woman should be tested for susceptibility to rubella by the HI test.

(*b*) If immune, she should be assured that vaccination is unnecessary.

(*c*) If susceptible, she may be vaccinated only if she understands that it is imperative for her to avoid becoming pregnant for the following 2 months. To ensure this, a medically acceptable method for pregnancy prevention should be followed. This precaution also applies to women in the immediate post-partum period. Additionally, she should be informed of the frequent occurrence of self-limited arthralgia and possible arthritis beginning 2 to 4 weeks after vaccination.

e. Use of Vaccine after Exposure to Natural Infection. There is no evidence that live rubella virus vaccine given after exposure will prevent illness. There is, however, no contraindication to vaccinating children already exposed to natural rubella. For women exposed to rubella, the concepts listed previously apply.

f. Precautions and Contraindications.

(1) Live rubella virus vaccine is contraindicated during pregnancy.

(2) Attenuated rubella virus infection might be potentiated by severe underlying diseases, such as leukemia, lymphoma, or generalized malignancy, and when resistance has been lowered by therapy with steroids, alkylating drugs, antimetabolites, or radiation. Vaccination of such patients should be avoided.

(3) Vaccination should be postponed until the patient has recovered from any severe febrile disease.

(4) Rubella vaccine is produced in cell culture. Care should be exercised in administering vaccine to persons with known hypersensitivity to the species from which the cells were derived (indicated in the labeling). The vaccine contains a small amount of neomycin and should not be given to individuals known to be sensitive to this antibiotic.

26. Immune Serum Globulin (Gamma Globulin).

a. General. Immune Serum Gloublin (Human) is a preparation containing the dominant (IgG or Gamma G) form of antibodies found in the blood of normal adult human beings. In practice it has been found to be of value in prophylaxis of infectious hepatitis, measles and, in a marginal sense, of poliomyelitis and rubella. Immune globulin preparations for measles, vaccinia, pertussis, and mumps and tetanus are obtained by hyperimmunization of human being or from persons with high antibody titers. The vaccinia immune globulin is available from Walter Reed Army Institute of Research and the American Red Cross. Vaccinia, pertussis and mumps immune globulins are available commercially as nonstandard items.

b. Material. Immune serum globulin is a clear, faintly straw colored or nearly colorless solution of the gamma globulin fraction, consisting almost entirely of human IgG ("gamma G") globulin prepared by ethanol fractionation of plasma at low temperatures. Immune serum globulins designated for specific disease entities such as vaccinia immune globulin and measles immune globulin are drawn from convalescent or hyperimmunized individuals and are tested to contain a minimum potency of specific antibody. Different preparations of gamma globulin contain variable trace amounts of autolytic enzymes so that they may undergo molecular fragmentation with storage; therefore the expiration date on gamma globulin preparations should be scrupulously observed.

c. Method of Use.

(1) *Measles.* The almost universal use of live attenuated measles vaccines has now reduced the indications for immune serum globulin (human) to those who are susceptible to measles, have been definitely exposed, and are considered to be subject to an unusual hazard, because of extreme youth, debility, steroid or irradiation therapy or other reasons. In such individuals prevention of measles should be attempted with a dose of 0.1 ml of gamma globulin per pound of body weight given intramuscularly *as soon as practical after exposure.* Unless there is a specific contraindication to the use of live attenuated vaccines in such individuals, they should subsequently be vaccinated against measles. However, the interval between injection of the gamma globulin and administration of live vaccines should be no less than three months, since otherwise the gamma globulin may interfere with the immunizing action of the vaccine.

(2) *Hepatitis.*

(*a*) *Infectious Hepatitis.* Intramuscular

injection of 5 ml. of gamma globulin is recommended for individuals exposed to an unusual risk of infectious hepatitis; areas or groups under such risk will be defined by the appropriate Surgeon General. This dose will prevent a large proportion of the expected clinical cases from occurring; a larger dose will somewhat prolong the duration of protection. Individuals known to have been exposed to infectious hepatitis have in some instances apparently had their disease prevented or modified when given this dose of gamma globulin as long as five weeks after exposure. Protection with this dose begins to fall off within 2 to 3 months. After 3 months subclinical hepatitis begins to occur with subsequent active immunity; if this has not occurred, protection is generally gone after 6 months. At this time, a second injection is given to those under continuing high exposure. This is not repeated since most individuals will have acquired active immunity under the conditions which justify this prophylaxis.

(*b*) *Transfusion Hepatitis.* There is no conclusive evidence that gamma globulin is effective in preventing this disease.

(3) *Poliomyelitis.* See TB MED 193/ NAVMED P 5052–2A/AFP 160–5–15.

(4) *Rubella.* Intramuscular administration of 20 ml. of immune serum globulin to a woman in the first trimester of pregnancy, as soon as possible after known exposure to rubella, has been used in an attempt to decrease the incidence of congenital malformations in the fetus. The degree of protection obtained depends on the titer of antirubella antibody; it is ineffective if given more than 6 days after exposure. Where accurate diagnostic facilities for rubella immunity are available, the susceptibility of such women should be determined by a serologic test prior to considering the injection of gamma globulin for this purpose.

(5) *Varicella.* Some lots of immune serum globulin administered within 3 days after exposure at a dose level of 0.6 ml. per pound of body weight have proven to be effective in modifying chicken pox. This is indicated in patients with blood dyscrasias, or on steroid, antimetabolite, alkylating agent or radiation therapy. Experimental sera obtained from zoster convalescent patients (zoster immune globulin) has been particularly effective.

(6) *Vaccinia Immune Globulin* (VIG). This product is given intramuscularly for the treatment of some complications of smallpox vaccination. It is of particular value in the treatment of eczema vaccinatum, in which case 0.3 ml. per pound of body weight is administered, and in vaccinia necrosum, where the recommended dose is 0.6 ml. per pound of body weight. It is only required for generalized vaccinia if the patient is particularly toxic and fever is high, in which case the dose is 0.15 ml. per pound. It is contraindicated in accidental infections, particularly of the eye, and in postvaccinal encephalitis. Among groups with a high incidence of postvaccinal encephalitis, vaccinia immune globulin has been used as a prophylactic; 2 ml. given intramuscularly at the same time as percutaneous vaccination does not interfere with the development of the reaction at the vaccination site, but has resulted in a marked reduction in the incidence of encephalitis. A similar dosage has been used to protect the eczematous child. Advice can be obtained by telephonic communication with the Director of the Division of Communicable Disease and Immunology, Walter Reed Army Institute of Research, or with one of the Vaccinia Immune Globulin Consultants of the American Red Cross. This material is available commercially and is also stocked at certain Red Cross centers, at the Walter Reed Army Institute of Research, at the 406th Medical General Laboratory, U.S. Medical Center, Japan, and in the USAREUR Medical Laboratory, Landstuhl, Germany.

d. Reactions.

(1) Immune serum globulin does not contain foreign protein and is, therefore, in the ordinary sense, nonantigenic in man. However, because of the antigenic differences in human gamma globulin allotypes, and because antibodies are formed against gamma G globulin aggregates, repeated injections may induce detectable antibodies against gamma globulin or these aggregates in some individuals. In addition, the product may contain preservatives or other substances to which an occasional recipient is sensitive. When prepared by the cold ethanol method, immune serum globulin has been shown to be free of infectious hepatitis virus.

(2) Immune serum globulin (human) must be administered intramuscularly. If given intravenously, the partially aggregated material may produce a severe shock-like reaction. Experimental preparations suitable for intravenous administration are under study.

APPENDIX A

BIOLOGICAL MATERIALS

(See section I, paragraph 3*a*)

Nomenclature	Federal stock No.	Unit	Dating period	Temperature for storage and after reconstitution
Cholera vaccine, USP, 20 cc	6505–160–1500	Btl	18 mo.	2°–8° C. (35°–46° F.)
Diphtheria and tetanus toxoids and pertussis vaccine, adsorbed, USP (pediatric use only)				
7.5 cc	6505–286–5349	Btl	18 mo.	Do.
Cartridge-Needle Unit, 0.5 cc, 20s	6505–926–9090	Pkg	18 mo.	Do.
Globulin, immune serum USP, 10 cc: Human	6505–153–8278	Btl	36 mo.	Do.
Globulin, tetanus immune USP, 250 units: Human	6505–890–1975	Btl	36 mo.	Do.
Globulin, tetanus immune USP, syringe and needle unit 250 units: Human	6505–142–8494	Pkg	36 mo.	Do.
Influenza virus vaccine USP 30 doses *	6505–180–6291**	Btl	18 mo.	Do.
Measles Virus Vaccine, live attenuated Edmonson strain, lyophilized, 0.5 cc. single dose, 10s.	6505–457–2701	Pkg	12 mo.	2°–8° C. (35°–46° F.)
Measles Virus Vaccine, live, attenuated Schwarz strain, lyophilized, 0.5 cc single dose, 10s.	6505–913–8557	Box	12 mo.	2°–8° C. (35°–46° F.)
Mumps virus vaccine, live, Jeryl-Lynn (B-level) strain, lyophilized, Equivalent to 0.5 cc, single dose.	6505–142–9203	Pkg	12 mo.	Do.
Plague vaccine, USP, E Medium, 20 cc	6505–935–1128	Btl	18 mo.	2°–8° C. (35°–46° F.)
Poliovirus vaccine, live, oral, USP, Types 1, 2, & 3				
10 doses	6505–782–2650	Pkg	12 mo.	Below 23° F. (−5° C.); after thawing, 2°–8° C. (35°–46° F.)
100 doses	6505–782–2651	Pkg	12 mo.	
Rabies vaccine, USP, brain tissue (Semple), 14 doses	6505–160–7875	Pkg	6 mo.	2°–8° C. (35°–46° F.)
Rabies vaccine, USP, duck embryo, 7 doses	6505–754–2727	Pkg	18 mo.	Do.
Antirabies serum, USP, 1000 units	6505–634–7279	Btl	24 mo.	Do.
Rubella Virus Vaccine, live, Cendehill Strain, lyophilized, 10 doses	6505–181–7187	Pkg	12 mo.	Do.
Rubella virus vaccine, live, Meyer-Parkman strain, lyophilized, 10 doses	6505–145–0180	Box	12 mo.	2°–8° C. (35°–46° F.)
Smallpox vaccine, USP, freeze-dried:				
10 doses	6505–656–0497	Pkg	18 mo.	Do.
20 doses	6505–935–3997	Pkg	18 mo.	Do.
100 doses	6505–903–8173	Pkg	18 mo.	Do.
For jet gun, 100 doses *	6505–926–4764	Pkg	18 mo.	Do.
Tetanus and diphtheria toxoids adsorbed, USP (for adult use)				
5 cc	6505–299–8296	Btl	24 mo.	Do.
30 cc *	6505–864–5249	Btl	24 mo.	Do.
Cartridge-Needle Unit, 0.5 cc, 20s	6505–926–9104	Pkg	24 mo.	Do.

See footnotes at end of table.

Nomenclature	Federal stock No.	Unit	Dating period	Temperature for storage and after reconstitution
Tetanus Toxoid absorbed, USP, Cartridge-Needle Unit, 0.5 cc 20s	6505–926–9105	Pkg	24 mo.	(35°–46° F.)
Tetanus Toxoid, USP				
7.5 cc	6505–680–2433	Btl	24 mo.	Do.
Cartridge-Needle Unit, 0.5 cc, 20s	6505–926–9091	Pkg	24 mo.	Do.
Typhoid vaccine, acetone inactivated, dried				
20 doses	6505–524–0408	Pkg	18 mo.	Do.
100 doses	6505–935–5879	Pkg	18 mo.	Do.
Yellow Fever vaccine, USP				
20 doses	6505–162–1520	Pkg	12 mo.	Store below 32° F.
100 doses *	6505–687–7890	Pkg	12 mo.	Do not freeze separate diluent

* Suitable for jet gun use.

** Formula reviewed annually. May necessitate change in FSN.

APPENDIX B

GUIDE TO POSTEXPOSURE PROPHYLAXIS FOR RABIES

1. Local Treatment of Wounds Involving Possible Exposure to Rabies

Recommended in all exposures:

a. First-aid treatment: Immediate washing and flushing with soap and water, detergent or water alone (recommended procedure in all bite wounds including those unrelated to possible exposure to rabies).

b. Treatment by or under direction of a physician:

(1) Adequate cleansing of the wound.

(2) Thorough treatment with 20% soap solution and/or the application of a quaternary ammonium compound or other substance of proven lethal effect on the rabies virus.

(3) Topical application and infiltration around the wound of antirabies serum.

(4) Administration, where indicated, of antitetanus procedures and/or antibiotics and drugs to control infections other than rabies.

(5) Suturing of wound not advised.

Where soap has been used to clean wounds, all traces of it should be removed before the application of quaternary ammonium compounds because soap neutralizes the activity of such compounds.

Benzalkonium chloride, in a 1 percent concentration, has been demonstrated to be effective in the local treatment of wounds in guinea pigs infected with rabies virus. It should be noted that at this concentration quaternary ammonium compounds may exert a deleterious effect on tissues.

Compounds that have been demonstrated to have a specific lethal effect on rabies virus in vitro (different assay systems in mice) include the following:

Quaternary ammonium compounds

0.1% (1:1000) benzalkonium chloride—mixture of alkylbenzdydimethylammonium chlorides

0.1% (1:1000) cetrimonium bromide—hexadecytrimethylammonium bromide

1.0% (1:100) Hyamine 2389—mixture containing 40% of methyldodecylbenzyltrimethylammonium chloride and 10% of methyldodecylxylylene bis(trimethylammonium chloride)

1.0% (1:100) methyl benzethonium chloride—benzyldimthyl(2-(2-(p-(1,1,3,3-tetramethylbutyl)tolyloxy)ethoxy)ethyl)ammonium chloride

1.0% (1:100) benzethonium chloride—benzyldimethyl(2(2-(p-1,1,3,3-tetramethylbutylphenoxy)ethoxy)ethyl)ammonium chloride

1.0% (1:100) SKF 1183—p-phenylphenacylhexamethylenetetrammonium bromide

Other substances

43–70% ethanol; tincture of thiomersal; tincture of iodine and up to 0.01% (1:10000) aqueous solution of iodine; 1% to 2% soap solutions.

2. Specific Systemic Treatment

Information on the following table is intended only as a guide; modifications may be warranted in special situations such as in rabies-free areas, or in an endemic area by bite of a species found not infected on adequate laboratory and field studies; with bites by "healthy" animals in enzootic areas, local treatment, serum and 3 daily doses of vaccine may suffice until the animal is shown to be rabid.

Specific Systemic Treatment

Nature of exposure	Status of biting animal whether vaccinated or not		Recommended treatment
	At exposure	During observation (10 days)	
I. No lesions; indirect contact	Rabid		None.
II. Licks:			
(1) Unabraded skin	Rabid		None.
(2) Abraded skin, scratches and unabraded or abraded mucosa.	(*a*) Healthy	Clinical signs of rabies or proven rabid (laboratory).	Serum [1] immediately start vaccine [2] at first sign of rabies in the biting animal.
	(*b*) Signs suggestive of rabies	Healthy	Serum [1] immediately, followed by vaccine.[2] Vaccine may be stopped if animal is normal on fifth day after exposure.
	(*c*) Rabid, escaped, killed or unknown		Serum [1] immediately, followed by vaccine.[2]
III. Bites:			
(1) Mild exposure	(*a*) Healthy	Clinical signs of rabies or proven rabid (laboratory).	Serum [1] and start vaccine [2] at first sign of rabies in the biting animal.
	(*b*) Signs suggestive of rabies	Healthy	Serum [1] immediately, followed by vaccine.[2] Vaccine may be stopped if animal is normal on fifth day after exposure.
	(*c*) Rabid, escaped, killed or unknown		Serum [1] immediately, followed by vaccine.
	(*d*) Wild (wolf, jackal, stray dog, fox, bat).		Serum [1] immediately, followed by vaccine.[2]
(2) Severe exposure (multiple, or face, head, finger or neck bites).	(*a*) Healthy	Clinical signs of rabies or proven rabid (laboratory).	Serum [1] immediately, start vaccine [2] at first sign of rabies in the biting animal.
	(*b*) Signs suggestive of rabies	Healthy	Serum [1] immediately, followed by vaccine.[2] Vaccine may be stopped if animal is normal on fifth day after exposure.
	(*c*) Rabid, escaped, killed or unknown		
	(*d*) Wild (wolf, jackal, stray dog, fox, bat).		Serum [1] immediately, followed by vaccine.[2]

[1] Serum in a single dose of 40 I.U./kg. body weight; part infiltrated into injured tissues.

[2] 14–21 daily doses of vaccine, followed by a booster dose 10 days and 20 or more days following the last daily dose of vaccine. (Modified from WHO Expert Committee Report, No. 321, 1966)

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